

**Three Essays on Food and Drug Administration's Postmarketing Studies on Prescription  
Drugs in the United States**

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# **Three Essays on Food and Drug Administration's Postmarketing Studies on Prescription Drugs in the United States**

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University of Pittsburgh, 2019

With a paradigm shift from an approval-oriented approach to a lifecycle management approach and increasing demand for expedited approvals and drug safety, the importance of postmarketing studies has been emphasized in drug regulatory and policy environment. This change is reflected in the increasing number of postmarketing studies and the passage of Food and Drug Administration (FDA) Amendments Act of 2007 which authorized FDA to require drug sponsors to conduct postmarketing safety studies. On the other hand, some concern that postmarketing studies are getting longer and larger, the cost of postmarketing studies is rising, but those studies might not yield important information on the safety and effectiveness of drugs. Yet, we know little about FDA's use of postmarketing studies and their value. Study One (chapter 1) examines postmarketing studies established between July 2008 and May 2016. Most noteworthy, there have been no increases in postmarketing studies during this period and that the duration and number of subjects involved have not changed. Study Two (chapter 2) assess the value of postmarketing studies with respect to public health impact as measured by changes in drug labeling. I found that withdrawal or discontinuation of a drug resulting from postmarketing studies is rare and a half of fulfilled postmarketing studies resulted in label changes. Study Three (chapter 3) addresses whether and how the availability of postmarketing study options affects the drug approval process by examining qualitative data from FDA drug advisory committee meeting transcripts and interviews. I found a few statements (3.5% of the transcripts) by advisory

committee members indicating that the prospect of postmarketing studies made them more likely to support approval of a specific drug. Interviews with FDA reviewers, former and current advisory committee members, and industry revealed quite divergent views about the influence of the availability of postmarketing studies.

## Table of Contents

Preface.....	xxii
<b>1.0 Study 1: Descriptive analysis on FDA’s Postmarketing Studies on Prescription</b>	
<b>Drugs .....</b>	<b>1</b>
<b>1.1 Introduction .....</b>	<b>2</b>
<b>1.2 Background and Literature.....</b>	<b>4</b>
<b>1.2.1 Background.....</b>	<b>4</b>
<b>1.2.1.1 Postmarketing Studies and Food and Drug Administration</b>	
<b>Amendments Act.....</b>	<b>4</b>
<b>1.2.1.2 Policy issues .....</b>	<b>10</b>
<b>1.2.2 Literature .....</b>	<b>13</b>
<b>1.3 Research questions, Methods, and Data.....</b>	<b>20</b>
<b>1.3.1 Research questions .....</b>	<b>20</b>
<b>1.3.2 Methods and Data .....</b>	<b>22</b>
<b>1.4 Findings .....</b>	<b>33</b>
<b>1.4.1 Overview of PMR/PMCs .....</b>	<b>33</b>
<b>1.4.2 Trends in the use of PMR/PMCs .....</b>	<b>35</b>
<b>1.4.3 Disease classes and Class actions .....</b>	<b>40</b>
<b>1.4.4 Expedited approvals .....</b>	<b>43</b>
<b>1.4.5 Designs and purposes of studies.....</b>	<b>47</b>
<b>1.4.6 Length and size of studies.....</b>	<b>51</b>
<b>1.4.7 Compliance .....</b>	<b>55</b>

1.5 Discussion and Conclusion.....	60
Bibliography for Study 1 .....	63
Appendix A for Study 1: Tables .....	66
Appendix B for Study 1: Figures.....	74
Appendix C for Study 1: Types of Studies .....	82
2.0 Study 2: Value of postmarketing studies: How Does FDA Utilize Drug Information Acquired Through Postmarketing Studies? .....	86
2.1 Introduction .....	87
2.2 Background and Literature.....	89
2.2.1 Background.....	89
2.2.1.1 Establishment and Process of Postmarketing Studies.....	89
2.2.1.2 FDA drug regulation policy changes.....	94
2.2.2 Literature.....	100
2.2.2.1 PMR/PMCs for expedited approvals and fulfillment of PMR/PMCs .....	101
2.2.2.2 Use of information from PMR/PMCs .....	103
2.2.2.3 Sources of evidence for regulatory actions .....	105
2.2.2.4 Value of PMR/PMCs .....	107
2.3 Research questions, Methods, and Data.....	108
2.3.1 Research questions .....	108
2.3.2 Data .....	110
2.3.3 Methods.....	116
2.3.3.1 Data formation .....	116

2.3.3.2 Conceptual framework.....	121
2.4 Results.....	127
2.4.1 Label changes and PMR/PMCs .....	127
2.4.2 Regulatory actions: Withdrawal/discontinuation, REMS assignment .....	133
2.4.3 Logit and Ordinal Logit models on Label Changes.....	134
2.4.3.1 Final models .....	136
2.4.3.2 Required and Study design (data quality).....	138
2.4.3.3 Biologics .....	139
2.4.3.4 Safety studies.....	140
2.4.3.5 Expedited approvals and new molecular entities (NMEs).....	141
2.4.3.6 REMS and BBW .....	142
2.4.3.7 The number of PMR/PMCs .....	143
2.4.3.8 Disease-therapeutic area .....	143
2.5 Discussion and Conclusion.....	144
Bibliography for Study 2 .....	153
Appendix D for Study 2: Tables .....	159
Appendix E for paper 2: Figures .....	172
Appendix F for paper 2: Descriptive analyses of PMR/PMCs and label changes .....	178
Appendix G for paper 2: Label change determination .....	182
G.1 Work process .....	182
G.2 Justification .....	184
G.3 Black Box Warnings.....	230
G.4 EXCEPTIONS.....	235



<b>G.5 EXCLUDED FROM SAMPLE.....</b>	<b>236</b>
<b>Appendix H for paper 2: Label changes (2009-2017) and PMR/PMCs.....</b>	<b>237</b>
<b>3.0 Study 3: The effect of postmarketing studies on drug approval process.....</b>	<b>241</b>
<b>3.1 Introduction .....</b>	<b>242</b>
<b>3.2 Background and Literature.....</b>	<b>244</b>
3.2.1 Drug lag and policy changes .....	245
3.2.2 Increasing demand for postmarketing studies .....	249
3.2.3 Policy issues amid the increasing postmarketing studies .....	254
3.2.4 FDA Advisory Committee .....	256
<b>3.3 Research questions, Methods, and Data.....</b>	<b>259</b>
3.3.1 Research questions .....	259
3.3.2 Methods.....	263
3.3.3 Data .....	265
<b>3.4 Findings .....</b>	<b>270</b>
3.4.1 PMR/PMC discussions in advisory committee meetings.....	270
3.4.2 Qualitative assessment on the role of PMR/PMCs on approval decisions from the meeting transcripts .....	273
3.4.3 Findings from interviews.....	281
3.4.3.1 Effect of PMR/PMCs on the approval process .....	281
3.4.3.2 Signaling postmarketing studies will be carried out .....	282
3.4.3.3 Role of the existence of alternative therapy on approval process ...	282
3.4.3.4 Increase in the number of PMR/PMCs .....	283
3.4.3.5 Enforcement .....	284

<b>3.5 Discussion and Conclusions .....</b>	<b>286</b>
<b>Bibliography for Study 3 .....</b>	<b>290</b>
<b>Appendix I for Study 3: Tables.....</b>	<b>297</b>
<b>Appendix J For paper 3: Figures .....</b>	<b>304</b>
<b>Appendix K for Study 3: Interview Data – Key comments .....</b>	<b>306</b>
<b>Appendix L for Study 3: Interview Questions .....</b>	<b>311</b>
<b>Appendix M for Study 3: Committee Comments on PMR/PMC-approval discussion.....</b>	<b>319</b>
<b>Appendix N for Study 3: PMS discussions and approval decisions by safety and efficacy (period 2).....</b>	<b>349</b>
<b>Appendix O for Study 3: The role of PMS in addressing uncertainties, for successful applications.....</b>	<b>352</b>
<b>Appendix P for Study 3: The role of PMS in addressing uncertainties, for re-submitted application .....</b>	<b>360</b>
<b>Appendix Q for Study 3: Examination of accelerated approvals and animal efficacy approvals.....</b>	<b>363</b>
<b>Appendix R for Study 3: Analyses on Advisory Committee Meeting Transcripts.....</b>	<b>367</b>

## List of Tables

<b>Table 1-1. Types of Postmarketing Studies and Statutes .....</b>	<b>6</b>
<b>Table 1-2. PMR/PMC status defined by the FDA.....</b>	<b>9</b>
<b>Table 1-3. Relevant Literature.....</b>	<b>19</b>
<b>Table 1-4. Example of PMR/PMCs: Cimzia.....</b>	<b>24</b>
<b>Table 1-5. PMR/PMC classification by study newness, function, design, and purpose .....</b>	<b>30</b>
<b>Table 1-6. PMR/PMCs by type, July 2008 – May 2016.....</b>	<b>34</b>
<b>Table 1-7. Major class actions, FDAAA safety studies.....</b>	<b>42</b>
<b>Table 1-8. Number of postmarketing studies by study type and number of expedited pathways designated for approvals .....</b>	<b>45</b>
<b>Table 1-9. Average length and size of PMR/PMCs, by expedited vs. traditional, by requirement vs. commitment, and by trials vs. observational.....</b>	<b>54</b>
<b>Table 1-10. Fulfilled and Pending/Delayed studies, by study design, requirement vs. commitment, and expedited vs. traditional (sample of the PMR/PMCs established Jul 2008 – Dec 2010).....</b>	<b>58</b>
<b>Table 1-11. Reasons of delays (sample size: 43) .....</b>	<b>59</b>
<b>Table A-1. Number of PMS by NDA and BLA by approval year, all new and supplemental approvals.....</b>	<b>66</b>
<b>Table A-2. Number of PMS by new and supplemental approvals .....</b>	<b>66</b>
<b>Table A-3. Number of postmarketing studies for expedited approvals by study type.....</b>	<b>67</b>
<b>Table A-4. Disease Classification.....</b>	<b>67</b>
<b>Table A-5. Number of postmarketing studies, by PMS types and by disease class .....</b>	<b>68</b>

<b>Table A-6. Number of postmarketing studies, by year and disease class .....</b>	<b>68</b>
<b>Table A-7. Variable description.....</b>	<b>69</b>
<b>Table A-8. Example of PMR/PMCs for Afinitor (NDA #22334) .....</b>	<b>72</b>
<b>Table 2-1. FDA’s postmarketing regulatory actions that can result from postmarketing studies.....</b>	<b>88</b>
<b>Table 2-2. Types of Postmarketing Studies and Statutes .....</b>	<b>90</b>
<b>Table 2-3. Number of PMR/PMCs established by CDER, FDA (2009-2015) .....</b>	<b>99</b>
<b>Table 2-4. PMR/PMC status defined by FDA .....</b>	<b>112</b>
<b>Table 2-5. Approvals in the 2008 sample .....</b>	<b>115</b>
<b>Table 2-6. Coding “label change” outcome rules and required evidence.....</b>	<b>119</b>
<b>Table 2-7. Label changes, comparing drugs with PMR/PMCs to drugs without PMR/PMCs .....</b>	<b>128</b>
<b>Table 2-8. Drugs with label changes, by fulfilled PMR/PMCs vs. unfulfilled PMR/PMCs, by BBW vs. Indication .....</b>	<b>132</b>
<b>Table 2-9. Descriptive Statistics.....</b>	<b>135</b>
<b>Table 2-10. Logit and OLogit Regression Results .....</b>	<b>137</b>
<b>Table 2-11. Predicted probabilities, by requirement and design.....</b>	<b>139</b>
<b>Table D-1. Sources of evidence for safety label changes in 2010 .....</b>	<b>159</b>
<b>Table D-2. Frequency analysis of drug safety communications by evidence source .....</b>	<b>159</b>
<b>Table D-3. Predicted probabilities, by requirement and design.....</b>	<b>159</b>
<b>Table D-4. Label changes by disease, excluding PREA.....</b>	<b>160</b>
<b>Table D-5. Label changes by FDA office/division, excluding PREA.....</b>	<b>160</b>
<b>Table D-6. Model test results .....</b>	<b>160</b>

Table D-7. Predicted probabilities, by NDA-BLA and requirement .....	162
Table D-8. Predicted probabilities, by requirement and safety.....	162
Table D-9. Variable descriptions .....	162
Table D-10. Drugs with label changes, by the existence of PMR/PMCs.....	164
Table D-11. Drugs with label changes, by BBW and Indication changes.....	165
Table D-12. Drugs with label changes, by fulfilled vs. unfulfilled PMR/PMCs .....	165
Table D-13. Logit/Ologit models with study of purpose.....	166
Table D-14. Label changes, comparing drugs with PMR/PMCs to drugs without PMR/PMCs (new drug approvals 2008-2010) .....	167
Table D-15. Cost estimation of FDAAA studies .....	167
Table D-16. Logit model results – safety label change vs. efficacy label change including PREA studies (N=110) .....	169
Table F-17. Label changes by postmarketing statutes .....	178
Table F-18. <i>PMR/PMCs and label changes by approval paths and REMS, excl. PREA</i> .....	179
Table F-19. PMR/PMCs and Label changes by study purpose, excluding PREA.....	180
Table F-20. <i>Label change by Data Source (study design), excluding PREA</i> .....	181
Table H-21. Drugs with label changes, with no further PMS since 2008, by previous PMS .....	238
Table H-22. Label changes, by previous PMS or without previous PMS.....	239
Table 3-1. Types of Postmarketing Studies and Statutes .....	244
Table 3-2. Committee meetings and drug approvals, by time-period and committee .....	267
Table 3-3. Advisory Committee (AC) meetings, postmarketing studies (PMS) discussed.	271
Table 3-4. Brief contents of discussion on postmarketing studies .....	275

<b>Table I-1. Safety event reports received by year, FAERS.....</b>	<b>297</b>
<b>Table I-2. Variable Descriptions.....</b>	<b>297</b>
<b>Table I-3. Advisory Committee Meetings by year and by committees .....</b>	<b>300</b>
<b>Table I-4. The number of AC meetings where PMS-approval was discussed .....</b>	<b>301</b>
<b>Table I-5. The number of AC with PMS discussion, by application types .....</b>	<b>301</b>
<b>Table I-6. Vote concordance .....</b>	<b>302</b>
<b>Table I-7. Characteristics of drugs discussed in ACs .....</b>	<b>302</b>
<b>Table I-8. Final decisions made by the FDA, among 24 drug approvals with PMR/PMC discussion .....</b>	<b>303</b>
<b>Table M-9. More detailed comments on PMS-approval discussion from the committee meetings .....</b>	<b>319</b>
<b>Table N-10. Drugs that had separate voting questions, Period 2 .....</b>	<b>350</b>
<b>Table O-11. The role of PMS in addressing uncertainties .....</b>	<b>352</b>
<b>Table P-12. Rationale for rejection and FDA’s final decisions on approval and PMR/PMCs .....</b>	<b>360</b>
<b>Table Q-13. Examination of accelerated approvals and animal efficacy approvals.....</b>	<b>363</b>
<b>Table R-14. FDA’s drug approval decision, by PMS mandatory or discretionary, Period 2 .....</b>	<b>372</b>
<b>Table R-15. PMS-mandatory drugs (AA and Animal), Period 2 .....</b>	<b>375</b>
<b>Table R-16. Drugs approved by FDA, amidst disagreement, in Period 2 .....</b>	<b>379</b>
<b>Table R-17. Approval decisions when the discussion was in the context of approval.....</b>	<b>382</b>
<b>Table R-18. Efficacy evidence and voting/approval results when postmarketing studies were discussed in relation to approval, for Period 2 only .....</b>	<b>385</b>

<b>Table R-19. Orphan and Non-orphan drug approvals .....</b>	<b>386</b>
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## List of Figures

Figure 1-1. Data Scope of this project.....	23
Figure 1-2. Data Sample.....	26
Figure 1-3. Time trend: Percentage of NMEs with at least one PMR/PMC (1970-2017) ....	36
Figure 1-4. The percentage of new drug applications (NDAs) with at least one PMR/PMC (1990-2016).....	36
Figure 1-5. Number of PMR/PMCs established 2009-20 .....	37
Figure 1-6. Number of PMR/PMCs, 2009-2015, by the timing of PMR/PMCs .....	38
Figure 1-7. Total number of PMR/PMCs and average number of PMR/PMCs per drug approval, 2009-2015.....	38
Figure 1-8. Total number of PMR/PMCs and number of PMR/PMCs without two most outstanding class actions .....	39
Figure 1-9. Total number of PMR/PMCs and the percentage of PMRs of total PMR/PMCs, by disease class .....	41
Figure 1-10. The number of new drug approvals with and without PMR/PMCs, by expedited or orphan designation.....	44
Figure 1-11. The percentage of drug approvals with PMR/PMCs and average number of PMR/PMCs per approval, by expedited_orphan status and year .....	47
Figure 1-12. PMR/PMCs by study design .....	48
Figure 1-13. Study design by PMR/PMC type (legal statute).....	49
Figure 1-14. Study purpose by PMR/PMC type .....	50
Figure 1-15. Average length and size of PMR/PMCs .....	53



<b>Figure 1-16. PMR/PMC status by study types (as of July 2018) .....</b>	<b>56</b>
<b>Figure B-1. Average number of PMS and % of drugs with PMS, new drug approvals (original NDA/BLAs), July 2008-May 2016.....</b>	<b>74</b>
<b>Figure B-2. Number of PMR/PMCs established, by chemical type (NME vs. non-NME)...</b>	<b>74</b>
<b>Figure B-3. PMR/PMC status by study design, as of July 2018 .....</b>	<b>75</b>
<b>Figure B-4. PMR/PMC status by establishment year.....</b>	<b>75</b>
<b>Figure B-5. The status of PMS established between July 2008 and December 2010 (sample size = 658).....</b>	<b>76</b>
<b>Figure B-6. PMR/PMCs by the source of sample .....</b>	<b>77</b>
<b>Figure B-7. Matrix by study design and study purpose .....</b>	<b>77</b>
<b>Figure B-8. The average number of PMS, by expedited or orphan, without Priority review designation .....</b>	<b>78</b>
<b>Figure B-9. The number of new drug approvals with PMS and without PMS, by expedited or orphan designation.....</b>	<b>78</b>
<b>Figure B-10. Percentage of PMS, the source of sample and PMS type.....</b>	<b>79</b>
<b>Figure B-11. The number of PMS by PMS categories (2009-2015) .....</b>	<b>79</b>
<b>Figure B-12. Percentage of NDAs with at least one PMR/PMC and Median approval time (standard review) .....</b>	<b>80</b>
<b>Figure B-13. Average length and size of PMR/PMCs and median approval time (standard review).....</b>	<b>80</b>
<b>Figure B-14. Trends on the percentage of study purpose, 2008-2016.....</b>	<b>81</b>
<b>Figure C-15. Nature of studies, by PMR/PMC type .....</b>	<b>82</b>

Figure 2-1. Time trend: Percentage of NMEs with at least one postmarketing study (1970-2016) .....	98
Figure 2-2. Study sample selection process.....	114
Figure 2-3. Drugs with label changes on BBW and indication, by the existence of PMR/PMCs .....	129
Figure 2-4. Drugs with label changes, by fulfilled PMR/PMCs vs. unfulfilled PMR/PMCs .....	131
Figure E-1. Contributions of Postmarketing Studies to Sponsors' knowledge base .....	172
Figure E-2. Label change initiator in 2010 .....	172
Figure E-3. The total number of postmarketing studies and label changes .....	173
Figure E-4. Predicted probabilities of label change (Logit on left, Ologit on right).....	174
Figure E-5. Predicted probabilities of label change by the number of postmarketing studies and Expedited approval paths .....	175
Figure E-6. Distribution for duration (label change date – PMR/PMC est. date) Left: including PREA, Right: excluding PREA .....	176
Figure E-7. Influence of product review factors on PMC decision (2008 BAH study), 2004-2007.....	176
Figure E-8. Fulfilled PMCs impact on Label changes (2008 BAH study), 2004-2007.....	176
Figure E-9. PMR/PMC Backlog by Year Established (BAH study, 2010), 2004-2007.....	176
Figure E-10. Spontaneous reports FDA received over time .....	177
Figure H-11. Label change sample, 333 out of total 1,226 label revision approvals.....	237
Figure H-12. Drugs with label changes, by previous PMS vs. without previous PMS .....	238
Figure H-13. Label changes, by previous PMS or without previous PMS .....	240

Figure 3-1. Percentage of NMEs with at least one postmarketing study, 1970-2017.....	253
Figure 3-2. Advisory meeting sampling .....	267
Figure J-1. Time trend: All expedited drug approvals, 1987-2014 .....	304
Figure J-2. The number of AC meetings by disease class (2000-2015), all ACs except for medical imaging products advisory committee.....	304
Figure J-3. Number of Advisory Committee meetings (1985-2015).....	304
Figure J-4. Ad Com recommendations and FDA approval decision .....	305
Figure J-5. Ad Com recommendations and FDA approval decision .....	305
Figure J-6. Total NMEs and NMEs with PMR/PMCs by therapeutic areas (1999-2015) .	305
Figure R-7. FDA’s decision on approval and PMS, by the committee votes, Period 2 .....	377
Figure R-8. Average percentage of for approval by PMS-approval discussion.....	380
Figure R-9. FDA final decision by PMS discussion and PMS-approval discussion, Period 2 .....	383

## List of Acronyms

AA	Accelerated Approval
AC	Advisory Committee
ADME	Absorption, Distinction, Metabolism, and Excretion
ANDA	Abbreviated New Drug Application
BAH	Booz Allen Hamilton
BBW	Black Box Warning
BLA	Biologic License Application
BT	Breakthrough Therapy
CBER	Center for Biologics Evaluation and Research, FDA
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research, FDA
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CSDD	Center for the Study of Drug Development (Tufts University)
DDI	Drug-Drug Interaction
EPC	Established Pharmacologic Class
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FD&C	Federal Food, Drug, and Cosmetic Act
FDAMA	Food and Drug Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FOIA	Freedom of Information Act
FT	Fast Track
GAO	U.S. Government Accountability Office
HHS	U.S. Department of Health and Human Services
ICD	International Classification of Diseases
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	Institutional Review Board
NCI	National Cancer Institute
NCE	New Chemical Entity
NDA	New Drug Application
NDC	National Drug Code
NIH	National Institutes of Health
NME	New molecular entity
ODA	Orphan Drug Act
OIG	Office of Inspector General, Department of Health and Human Services
OND	Office of New Drugs, CDER, FDA
OTC	Over-The-Counter
PDUFA	Prescription Drug User Fee Act

PE	Physiologic Effect
PK	Pharmacokinetic
PD	Pharmacodynamic
PMC	Postmarketing Commitment
PMPY	Per Member Per Year
PMR	Postmarketing Requirement
PMS	Postmarketing Study
PMT	Postmarketing Trial
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy

## Preface

I am deeply indebted to my advisor, John M. Mendeloff. His mentorship and advice was profound. He always made himself available for our discussions and debates. His planet-size and sharp policy mind sometimes intimidated me, yet inspired me greatly. His questions often challenged and amazed me because those questions led to new ideas that, in turn, became crucial part of my research. John also has been very understanding and patient with my learning and procrastination as well as personal struggles. Many students meet with difficulties over the course of PhD program for various reasons and I wasn't an exception. John has supported my journey all the way through. Without his support and nurturing, the completion of my dissertation would not have been possible.

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Lastly, I dedicate this thesis to God. He was my father, teacher, guide, and friend along the way.



## **1.0 Study 1: Descriptive analysis on FDA's Postmarketing Studies on Prescription Drugs**

### **Abstract**

Postmarketing studies have become a significant feature of the drug approval process in the United States. They represent one tactic in the attempt to resolve conflicts between faster approval of new drugs and the need to ensure their safety and efficacy. In particular, postmarketing studies pursue the objective of a life-cycle approach to drug regulation, rather than one that focuses so heavily on initial approval decisions. This paper examines postmarketing studies established by the Food and Drug Administration (FDA) between July 2008 and May 2016. I examine 1) trends in the percentage of drugs with postmarketing studies and the average number of studies per drug; 2) variations in the use of postmarketing studies with different disease categories and with different categories for expediting approvals; 3) trends in the duration of postmarketing studies and the number of people they study; and 4) trends in the percentage of studies fulfilled. Most noteworthy, there have been no increases in postmarketing studies during this period and that the duration and number of subjects involved have not changed.

## 1.1 Introduction

The Food and Drug Administration (FDA) evaluates new drug and biological products prior to approval for marketing in the United States in order to ensure the products' efficacy and safety for human use. However, although the FDA approves a drug, a number of issues may remain unresolved. Thus, the FDA may request or require that a sponsor seeking approval of a new drug conduct a postmarketing study to provide additional information that is important in assessing benefit and risk of the drug. In a number of cases, these studies are required by law.

In September 2007, Congress passed the FDA Amendments Act (FDAAA), which authorized the FDA to require certain postmarketing studies and clinical trials<sup>1</sup> of prescription drugs and mandate adherence to study deadlines (FDA, 2011). This new authority became effective on March 2008.<sup>2</sup> The FDAAA of 2007 was a significant step to provide more information about safety and effectiveness of drugs after approval, but it was only a step in a longer-term upward trend in the use of postmarketing studies.

Since the 1990s, increasing expedited approvals driven by public demand for faster access to drug therapies and the introduction of Prescription Drug User Fee Act (PDUFA) have made postmarketing studies and surveillance more desirable. Moreover, Vioxx, Avandia, Selective Serotonin Reuptake Inhibitors (SSRIs), and other drug-related safety events spurred public debate

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<sup>1</sup> FDAAA makes a distinction between “study” and “clinical trial.” Previous laws, regulations, and practice generally used the terms studies and trials interchangeably. For example, section 506B of the Act (21 U.S.C. 356b) uses “studies” to describe the postmarketing commitments (PMCs) that must be reported annually, including clinical trials. Hereinafter, I use the term “study” for both clinical trials and non-clinical-trial studies in this document unless the distinction is necessary. Thus, postmarketing studies include postmarketing requirements (PMR) and postmarketing commitments (PMC) in trial, observational, and non-clinical settings.

<sup>2</sup> <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm064633.htm>

on drug safety (Institute of Medicine [IOM], 2007; IOM, 2012). As a result, the political demand for postmarketing regulation and postmarketing research has risen.<sup>3</sup>

This environment shifted a drug regulation paradigm from an approval-oriented approach to a lifecycle management approach. The rationale for the lifecycle approach is that our understanding of benefits and risks of a drug changes over the drug's lifecycle and that the attention to the benefit and risk profile of the drug should be sustained throughout the lifecycle (FDA, 2004). This paradigm shift emphasizes the importance of postmarketing studies all the more. This paradigm shift is getting further driven and implemented by the FDA commissioner (since May 2017), Scott Gottlieb, who emphasized the role of postmarketing surveillance as follows<sup>4</sup>:

*“...It means shifting much more of the emphasis on active surveillance as opposed to FDA’s historically more binary approach to regulation that transfers most of the responsibility to the pre-market review process.”* (Gottlieb, 2016)<sup>5</sup>

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<sup>3</sup> Political demands can be seen in Congress and FDA’s responses. (1) Soon after rofecoxib’s withdrawal in 2004, hearings of the Senate Finance Committee and media raised serious questions about drug safety. In response, CDER asked the IOM to assess the U.S. drug-safety system which was published in 2006. (2) In 2005, the FDA formed the Drug Safety Oversight Board to advise the CDER, which was IOM’s recommendation. (3) PDUFA III (2002) and IV (2007) expanded budget appropriation for postmarketing regulation on drug safety. (4) Congress passed the FDAAA of 2007 that greatly emphasizes the role of postmarketing regulations for the drug safety such as requiring postmarketing studies, labeling revisions, and Risk Evaluation and Mitigation Strategies (REMS). (5) Congress passed Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 that expands FDA authorities to collect user fees to fund reviews of innovator drugs, introduces breakthrough therapy, and enhances the safety of the drug supply chain.

<sup>4</sup> “Update and modernize FDA’s approach to applying evidentiary standards for establishing safety and effectiveness for new drugs to more clearly define the role of real-world data and evidence....Explore the development of a policy framework under which an accelerated approval approach could be used to support marketing of a drug that demonstrates a survival benefit early in clinical development. The goal is to expedite availability of a therapy while the magnitude of the benefit it provides is being confirmed.....Advance the use of new drug development tools and mobile technology for better capturing clinical trial data and the measurement of safety and benefit in pre- and post-market settings.” In FDA’s 2018 Strategic Policy Roadmap (2018)

<sup>5</sup> <https://www.forbes.com/sites/scottgottlieb/2016/01/12/fda-needs-to-change-how-it-regulates-novel-technologies/2/#784ded13205f>

Given the importance of postmarketing studies in drug regulation in the United States, this paper aims to characterize several important features of postmarketing requirements (PMRs) and commitments (PMCs) that have been established since July 2008, following the expansion of FDA's authority under the FDAAA of 2007. I have collected information via Freedom of Information Act (FOIA) requests to the FDA on all postmarketing studies established by the FDA since that year along with information on all drug approvals.

This paper is a descriptive study that aims to shed light on the trends of PMR/PMCs since the FDAAA. Specifically, I examine 1) trends in the percentage of drugs with postmarketing studies and the average number of studies per drug; 2) variations in the use of postmarketing studies by disease categories and approval paths (expedited vs. traditional); 3) trends in the duration and size of postmarketing studies; and 4) trends in the percentage of studies fulfilled.

## **1.2 Background and Literature**

### **1.2.1 Background**

#### **1.2.1.1 Postmarketing Studies and Food and Drug Administration Amendments Act**

The FDA gets more than a thousand investigational new drug (IND) applications a year. From 2014 to 2017, on average, the Center for Drug Evaluation and Research (CDER) at the FDA received 1,610 new INDs. The Agency reviews clinical and non-clinical data from pre-approval studies to judge the safety and efficacy of those applications. Each year, the FDA approves hundreds new drug applications (NDAs) and biologic license application (BLAs): on average, CDER approved 121 NDA/BLAs each year during 2014-2017.

Additional studies are sometimes conducted following the FDA’s approval of a NDA or BLA, “during general use of the drug by medical practitioners” (Lipsky and Sharp, 2001). These studies are referred to as postmarketing studies (Lipsky and Sharp, 2001)<sup>6</sup> and these studies are funded by sponsors.

A postmarketing requirement is a study that the FDA mandates as a condition for approval as defined in section 901 of the 2007 FDAAA<sup>7</sup>. A study that is not required by statute might be conducted because a sponsor and the FDA agree, in writing, that such study should be conducted. This is a postmarketing *commitment*. (Table 1-1)

Not all of the postmarketing studies regulated by the FDA concern clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology: for example, some postmarketing studies deal with chemistry, manufacturing, and control issues. These studies are not required to be reported to the FDA under Code of Federal Regulation (CFR) Title 21 314.81(b)(2)(vii) and 601.70(a) (506B reporting requirement). See Figure 1-1 in Section 1.3.2.

Also, there are post-approval research activities that do not involve the FDA and they are considered voluntary studies and trials. For example, a sponsor may voluntarily create a clinical outcome registry. In this case, the registry is not regulated by the FDA, unless FDA becomes aware of new safety information and requires the sponsor to conduct a PMR study utilizing the registry data. These voluntary studies are not regulated by FDA.

Table 1-1 shows the types of postmarketing requirements by legal statutes. The postmarketing studies that can be required under FDAAA join the types of postmarketing studies

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<sup>6</sup> These studies are referred to as phase-4 studies as well. But, today, “postmarketing study” is more commonly used.

<sup>7</sup> Section 901 of the 2007 FDAAA created section 505(o) of the FD&C Act that states that the FDA can mandate PMRs in certain situations such as to confirm clinical benefit when a drug has been given “accelerated approval,” to assess risk associated with the drug, or to examine pediatric populations.

that FDA could require before FDAAA. Before FDAAA, FDA could require the following postmarketing studies<sup>8</sup>:

- Postmarketing studies to demonstrate clinical benefit for drugs approved under the accelerated approval requirements in 21 CFR 314.510 and 21 CFR 601.41 (Confirmatory studies for accelerated approval)
- Deferred pediatric studies (21 CFR 314.55(b) and 601.27(b)), where studies are required under the Pediatric Research Equity Act (PREA)
- Postmarketing studies to demonstrate safety and efficacy in humans that must be conducted at the time of use of products approved under the Animal Efficacy Rule (21 CFR 314.610(b)(1) and 601.91(b)(1)) (Animal studies)

**Table 1-1. Types of Postmarketing Studies and Statutes**

	Requirement (PMR)	Commitment (PMC)
Laws/Rules	<ul style="list-style-type: none"> <li>• Animal Efficacy: 1999 Animal Rules<sup>9</sup></li> <li>• Accelerated Approval: 1992 Accelerated Rules<sup>10</sup></li> <li>• Pediatric Studies: 2003 Pediatric Research Equity Act (PREA)<sup>11</sup></li> <li>• Safety studies<sup>12</sup>: 2007 FDAAA<sup>13</sup></li> </ul>	1997 FDAMA <sup>14</sup> (Agreed-upon postmarketing studies that do not meet the statutory criteria for PMRs)
Enforcement	Charges under section 505 of the Act Misbranding charges (section 502(z)) Civil monetary penalties (section 303(f))	No enforcement

<sup>8</sup> <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>

<sup>9</sup> 21 CFR 314.610(b)(1), Subpart I (drugs); 21 CFR 601.91(b)(1), Subpart H (biologics)

<sup>10</sup> 21 CFR 314.510, Subpart H (drugs); 21 CFR 601.41, Subpart E (biologics)

<sup>11</sup> 21 CFR 314.55(b) (drugs); 21 CFR 601.27(b) (biologics)

<sup>12</sup> Section 505(o) of the Act states that postmarketing studies and clinical trials may be required for any or all of three purposes related to risk:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

<sup>13</sup> Section 505(o)(3) of the FDCA

<sup>14</sup> 21 CFR 312.85

Under FDAAA, postmarketing studies also can be required to<sup>15</sup>:

- Assess a known serious risk related to the use of the drug
- Assess signals of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Another change brought by FDAAA is the distinction between postmarketing requirements (PMR) and commitments (PMC). In 1997, when the Food and Drug Administration Modernization Act (FDAMA) was passed, the Modernization Act required sponsors of approved drugs to report to FDA on the progress of their postmarketing commitments, which was defined to include required studies—confirmatory studies for accelerated approvals, PREA studies, and animal studies—and agreed-upon commitments. Now, under the FDAAA of 2007, commitments and requirements are treated differently because section 505 created safety requirements—some of the requirements would have been commitments before the FDAAA.

The PMR/PMC development process typically occurs during the NDA/BLA review phase. According to a Booz Allen Hamilton study (2008) the PMC development process (is generally initiated when a data gap or issue is identified, which typically happens early in the review process.<sup>16</sup> (Note that this study examined only PMCs.) Once an issue was identified, FDA

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<sup>15</sup> <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>

<sup>16</sup> BAH (2008) says that “82% of issues were identified after application submission and before the end of the review phase”

discussed the PMC with the sponsors<sup>17</sup> and the PMC is documented in the action letter (approval letter<sup>18</sup>). Then, the FDA tracks and reviews PMC activities; the Agency reviews sponsor-submitted materials and communicates with sponsors as needed.

After the final postmarketing report is submitted, the FDA decides whether a PMR/PMC is fulfilled. According to the FDA's guidance document<sup>19</sup>, if the FDA concludes that the study commitment has been met, it will notify sponsors that the commitment is fulfilled. If a study was completed but failed to satisfy the purpose of the study, but would still provide useful information and can be addressed through a study of modified design, the Agency may release the original commitment and establish a new PMR/PMC and schedule. If the FDA agrees that the failed study is no longer feasible or would not provide useful information, the FDA may release the PMR/PMC. If a study is terminated and the FDA determines is still feasible, would yield useful information, and can be addressed through a study of modified design, the Agency may release the original study and establish a new postmarketing study and schedule. If the FDA agrees the terminated study is no longer feasible or would not provide useful information, the FDA may release the study. A description on each PMR/PMC status is provided in Table 1-2 below.

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<sup>17</sup> BAH (2008) says that "once an issue was identified, FDA occasionally notified the sponsor of the issue before making the decision to address it as a PMC; however, in many cases FDA did not discuss the gap in product information with the sponsor until after the PMC decision point. The PMC decision point occurred most often in the review phase (59%), but also occasionally in the action phase (23%). Despite this relatively early PMC decision point, sponsors were more likely to be notified of the PMC late in the review, during the action phase (65%), than in the review phase (33%)."

<sup>18</sup> "An action letter is a letter to an applicant that is issued after the complete review of a filed application..... FDA issued an action letter (not approvable, approvable or approval letter) after a complete review of the application. If not an approval, the action letter contained a complete list of deficiencies in the application and completed the review cycle for the application. The next review cycle (resubmission) began when the agency receive a complete response to all deficiencies listed in the letter."

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172134.pdf>

<sup>19</sup> <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>



**Table 1-2. PMR/PMC status defined by the FDA**

Status	Description
Fulfilled	FDA has reviewed the PMR/PMC final report and notified the sponsor that the PMR/PMC has been satisfied
Submitted	The sponsor has concluded or terminated the study and has submitted a final study report to the FDA, but FDA has not yet notified the applicant in writing that the study commitment has been fulfilled or released
Released	FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study because the study is either no longer feasible or would no longer provide useful information.
Terminated	The applicant ended the study before completion and has not yet submitted a final study report to the FDA.
Ongoing	The study is proceeding according to, or is ahead of, the original schedule. The FDA considers a study to be ongoing until a final study report is submitted to the FDA, as long as the activities are proceeding according to the original study schedule. If patient accrual or animal dosing has started but is not complete, and the projected date for completion of that milestone has passed, the study should be categorized as delayed.
Delayed	The progression of the study is behind the original study schedule. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final study report to the FDA. While the original study schedule — not a revised schedule — serves as the basis for defining a study as delayed, each phase of the study will be considered in its own right. If the applicant has one delayed phase, but gets back on schedule during the next phase, the delayed status will no longer apply.
Pending	The study has not been initiated (i.e., no subjects have been enrolled or animals dosed), but does not meet the criterion for delayed (i.e., the original projected date for initiation of patient accrual or initiation of animal dosing has not passed).

[source: FDA guidance: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070799.htm>]

And, finally, the FDA reviews a supplemental application (for labeling revision) if the application is accompanied with the final report. The FDA manual (MAPP 6010.2)<sup>20</sup> says that “a final report submitted as a supplemental application will be reviewed according to established review times for supplements. A final report submitted without a supplemental filing should be reviewed within 1 year of receipt.” If a supplemental application for labeling revision was not

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<sup>20</sup> Manual of Policies And Procedures, MAPP 6010.2, Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments, CDER/FDA  
<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM174552.pdf>

accompanied, the FDA or sponsor could still change the drug label and post the findings from postmarketing studies to communicate with patients and doctors (Drug Safety Communications).<sup>21</sup>

### 1.2.1.2 Policy issues

Since the 1970s, more drugs have been approved with postmarketing requirements and/or commitments. However, the growth in postmarketing studies has stoked some policy controversies. First, some worry that the increasing cost of clinical research may make the industry more risk-averse and less willing to take challenges on novel drugs (Collier, 2009). The Tufts Center for the Study of Drug Development (CSDD) estimated that a postmarketing requirement costs \$3.7 million on average in 2003; conducting a postmarketing (phase 4) trial costs \$20 million<sup>22</sup> on average according to Sertkaya et al. (2014).<sup>23</sup> Postmarketing studies and trials can be a burden on small and mid-size pharmaceutical and biomedical firms, and this may result in decreases in drug innovation.

Those who argue that the high cost of postmarketing studies would decrease drug innovation assume that having a postmarketing study option would not affect drug approval

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<sup>21</sup> On a separate note, PREA studies are recognized as “fulfilled” when labeling revision application is accompanied with the final report. It is because the purpose of PREA is to update drug labels for children. The FDA usually doesn’t change the status of a PREA study unless the sponsor submits the proposed labeling revision because the purpose of PREA is to label drugs for children adequately. For example, on PMR/PMC status description about KEPPRA (LEVETIRACETAM)100MG/ML INJECTION (NDA #21872), the agency noted, “The final study report was submitted to FDA on January 31, 2011. However, UCB has not yet submitted the report of this required pediatric postmarketing study as a new drug application (NDA) or as a supplement to their approved NDA with the proposed labeling changes they believe are warranted based on the data derived from this study. Because the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) requires this accompanying submission to the PMR final study report, this PMR is therefore considered delayed.”

<sup>22</sup> <http://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development> On average, phase 4 trials cost \$20 million, but it varies by therapeutic areas: Anti-Infective \$11 million, Cardiovascular \$28 million, Central Nervous System \$14 million, Dermatology \$25 million, Endocrine \$27 million, Gastrointestinal \$22 million, Genitourinary \$7 million, Hematology \$27 million, Immunomodulation \$20 million, Oncology \$39 million, Ophthalmology \$18 million, Pain and Anesthesia \$32 million, and Respiratory \$73 million

<sup>23</sup> Sertkaya study (HHS study) in 2014 only estimated the cost of trials. It wouldn’t include any other study design—nonclinical toxicology, in-vitro studies, observational studies, etc. CSDD study includes any of these study designs thus the two cost estimations differ.

decisions. One might argue that the cost of postmarketing studies to firms may not be justifiable unless they get some benefit in terms of earlier drug approval. If there is no earlier approval, what benefit would PMR/PMCs provide to firms? And, if having the option of PMR/PMCs increases the odds of approval by minimizing the error costs of approval decision, some might pose a question whether and to what extent PMR/PMCs address the issues that are likely to occur in the postmarketing setting.

There is a concern about whether FDA's faster approval could increase the potential for previously unrecognized safety issues to appear once those drugs are widely used and postmarketing studies are not fulfilled (Darrow et al., 2014; Moore and Furberg, 2014; Carpenter et al., 2008; Carpenter et al., 2012). U.S. Government Accountability Office (GAO) [2009; 2015] reported that FDA's monitoring and enforcement associated with expedited approval process lacks consistency and accuracy. A recent study by Moore and Furberg (2014) found that "expedited reviews were approved more rapidly.... but considerably fewer patients were studied prior to approval, and many safety questions remained unanswered."<sup>24</sup>

The concern is growing because FDA's effort in accelerating drug development is expanding. More recent discussions (possible options in the near future) include alternative pathways, enriched trials, an innovative program for biomedical innovation, and reduced efficacy standards for Alzheimer disease<sup>25</sup> (FDA, 2014; Moore and Furberg, 2012; Carpenter, 2014).<sup>26</sup> The

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<sup>24</sup> Moore and Furberg studied 20 therapeutic drugs. Efficacy testing in the drugs with accelerated approvals was conducted on less than 1/5 of the median number of patients than standard review drugs. Of the 86 PMRs, 26 had been fulfilled more than 4 years after approval.

<sup>25</sup> Historically, FDA required two endpoints to be tested: cognition and function. In February 2018, FDA published new guideline about single endpoint.  
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf>

<sup>26</sup> Alternative pathways expedite the development of drugs by accepting studies in a smaller subpopulation of patients and labeling narrower indications in limited, well-defined subpopulations. Enriched trials allow patient selection before randomization based on the likelihood of response to the intervention.

Agency published guidance on some of these programs mostly during 2018-2019.<sup>27</sup> Kesselheim et al. (2015) concluded that there is “an increasing prevalence of expedited development and review programs that cannot be attributed to an increase in the number of innovative new drug classes over time. Though these programs were designed as exceptions...for...serious or life-threatening diseases, ..., a majority of [new] drugs were associated with at least one of these special programs, meaning that the exceptions had become more common than the rule.”<sup>28</sup>

Thus, the extent of enforcement of PMR/PMCs is part of a current policy debate because enforcement may be crucial for realizing the benefit of PMR/PMCs. GAO reported that 36% of required studies for drugs approved with surrogate endpoints between 1992 and 2008 were not completed (GAO, 2009).<sup>29</sup> Johnson et al. (2011) also reported that it took 0.8 to 12.6 years for sponsors to complete postmarketing trials for a sample of oncology drugs (35 oncology products for 47 new indications) approved under accelerated approval. The median time between accelerated approval and full approval of oncology products was 3.9 years and the mean time was 4.7 years.

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<sup>27</sup> Adaptive trial designs (FDA guidance in September 2018), enrichment strategies (FDA guidance in March 2019), efficient design for cancer drugs (FDA guidance in Sep 2018), allowing single endpoint for Alzheimer’s Disease (FDA guidance in Feb 2018), and pathogen-focused approach and streamlined programs for antibacterial therapies (FDA guidance in August 2017).

<sup>28</sup> Note 1: Kesselheim et al. (2015) found a significant increase of 2.6% per year in the number of expedited approvals from 1987 to 2014. [Figure 2 for time trend] And, according to FDA, 45% of new drugs were approved on the basis of a surrogate endpoint between 2010 and 2012 (FDA, 2015).

Note 2: 45% of new drugs were approved on the basis of surrogate markers, but recent studies (Kim and Prasad, 2015; Kim and Prasad, 2016; Prasad et al., 2015) show that the use of surrogate endpoints for oncologic drug approvals often lacks empirical verification of the strength of the surrogate-survival association and most cancer drug approvals have not been shown or do not improve clinically relevant endpoints.

<sup>29</sup> Of 144 postmarketing confirmatory studies associated with these 90 applications, as of December 19, 2008, 92 studies were closed (64%) and 52 were still open (36%). Among 52 open PMR/PMCs, 10 were delayed (19%) and 7 were pending (13%). Pending studies had been open, on average, for about 5.5 years, with more than 40 percent pending for over 8 years. In addition, studies classified as ongoing and delayed had been open, on average, for 5.3 and 4 years respectively, and those classified as submitted have been open on average about 5.6 years. (GAO, 2009)

In sum, the policy issues<sup>30</sup> related to postmarketing studies are the followings: (1) costs of postmarketing studies may impede drug innovation; (2) faster approval with less clinical testing and quicker review may make it more difficult to consider risks of drug; and (3) more expedited programs are being implemented that can lead to faster approval. Postmarketing studies are designed to be a safeguard, but often not getting fulfilled on time.

### 1.2.2 Literature

A table of major literature is provided at the end of this section (Table 1-3). Researchers have looked at FDA's monitoring, managing, and enforcing postmarketing commitments and requirements. Recent studies were carried out by Wallach et al. (2018), the Department of Health and Human Services Office of Inspector General (OIG) [2006, 2016], GAO (2015), and Booz Allen Hamilton (BAH) [2008]<sup>31</sup>.

The most relevant study was conducted by BAH in 2008. It analyzed postmarketing commitments associated with new drug applications, biologics applications, and supplements approved during FY2002 - FY2005. The BAH study agreed with OIG about FDA's lack of tools for monitoring and managing postmarketing studies and its lack of ability to enforce such commitments. The major findings from the BAH study included:

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<sup>30</sup> On another account of policy issues related to postmarketing regulation, one might argue that the FDA faces problems of protecting the public for almost absolute safety. No single regulatory system can guarantee absolute safety or effectiveness. This is an impossible task, but the public expects nearly absolute safety. For example, in their book *Perspectives on Risk and Regulation: The FDA at 100*, Daemmrich and Radin (2007) writes "During the century since the passage of the 1906 Federal Food and Drug Act the public has come to expect nearly absolute safety when consuming the products of science-based firms." Moreover, FDA's own credibility may be shrunk when approving bad drugs and when postmarketing regulation fails to ensure public health. The Agency's regulation power may depend on its credibility (in other words, reputation) and drug regulatory effect may be at stake if the agency reputation decreases (Carpenter, 2014; Carpenter and Krause, 2014).

<sup>31</sup> The FDA contracted with Booz Allen for an independent analysis of FDA's postmarket processes and procedures in order to improve the process for developing and tracking postmarket requirements and commitments.

- (1) Postmarketing study development: FDA reviewers often identified issues leading to PMCs early in the review process, but sponsors were typically not informed of PMC requests until the action phase, sometimes only days before the action date.<sup>32</sup> The timing of sponsor notification sometimes left insufficient opportunity for sponsors to evaluate study feasibility, clarify rationale and/or propose alternative study designs to achieve the desired goals. BAH noted that this might be associated with a greater number of delayed, terminated, or released PMCs.<sup>33</sup>
- (2) Expedited review drugs: Booz Allen found that drugs approved with priority review, orphan drug designation, fast track, and novelty were more likely to have PMCs than other approved drugs. The explanation was twofold: 1) FDA “reviewers take into account the potential benefit of a drug when determining whether an issue can be resolved post-approval”; and 2) novel drugs “are likely to have more unknowns, which would also explain the greater number of issues to resolve in the postmarketing phase.” This second reason implies that those expedited drugs have bigger potential risk than traditional review drugs. And, if a safety postmarketing study is needed, those drugs with bigger potential risk would be likely to have PMRs rather than PMCs compared to traditional review drugs.

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<sup>32</sup> The action phase includes the final steps of the review cycle through the action taken on the application, including the wrap-up meeting, compilation of the action package, and signatory authority review of the action package and action letter. The action date is the date FDA officially finalizes the decision and send the letter— complete response letter, approval letter, or withdrawal after filing letter.

<sup>33</sup> “Delayed PMCs were present in almost all study types and review divisions/offices, but one factor that appeared to contribute to the delayed status was the timing of sponsor notification of the PMC during the application review. ... most data gaps that became PMCs were identified early in the review, but sponsors were most often notified of the PMC request in the final weeks or days prior to the action date. In the study cohort, PMCs for which the sponsor was notified in the action phase were more frequently delayed than those in which the sponsor was notified during the review phase or earlier. This observation is consistent with sponsor comments that late notification of PMC requests made it more difficult to evaluate study feasibility and contributed to the difficulty in meeting milestones on time.”

(3) Comparison of views from FDA review team and sponsors on the rationale for PMCs and the impact of PMCs: The FDA review team and sponsors agreed that the PMCs they were involved with were appropriately deferred to postmarketing commitments rather than required as part of the preapproval testing. The most frequent reason given was that the lack of information was not important enough to cause the product not to be considered safe or effective, but was important to know for the optimal use of the product (33%).<sup>34</sup>

OIG (2006) examined the extent to which new drug applications involve postmarketing commitments with the FDA and how and to what extent the FDA monitors open commitments. It used the FDA database that included postmarketing studies associated with new drug applications approved during FY1990-FY2004. Note that there was no clear distinction between requirements and commitments before 2007 (other than pediatric studies and confirmatory trials for accelerated approvals, all postmarketing studies were called “commitments” before the 2007 FDAAA.) The OIG study confirmed that the percentage of NDAs with at least one commitment has increased since 1990 and new molecular entities (NMEs)<sup>35</sup> are associated with more commitments than non-NMEs. It also found that the FDA lacked effective and efficient tools for monitoring and managing PMCs because information was missing or incomplete and monitoring was a low priority within Center for Drug Evaluation and Research (CDER), FDA.

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<sup>34</sup> Other reasons include the following: (1) the issue was theoretical concern. It was not identified from information supplied in the product application, but was based on the reviewer’s experience (15%); (2) the issue required long-term data, generally five or more years worth of product use, which was not practical to collect prior to product approval (14%); and (3) the issue was expected to impact a small subpopulation of the users; this concern was sometimes noted on the product labeling (10%).

<sup>35</sup> An NME is a drug that contains an active moiety that has never been approved by the FDA or marketed in the U.S. The term NME is not defined in the statute or regulations.

Ten years later, OIG conducted a follow-up investigation to shed light on its previous work in consideration of FDA's expanded authority after the FDAAA of 2007. In its 2016 study, OIG reported that the earlier problems with data management and work process persisted despite some progress. OIG looked at 1,256 PMRs for prescription drugs initiated between 2008 and 2014. It found that FDA's reviewing annual status reports from sponsors took long and showed lack of ability to track PMRs. But, OIG noted some progress: fewer studies were delayed and sponsors are making progress toward completing most postmarketing requirements, and 23% of all PMRs were fulfilled in FY 2014.<sup>36</sup>

The findings of a GAO report published in 2015 mostly agreed with OIG. GAO said that the FDA's internal management of data failed to monitor the completeness, timeliness, and accuracy of postmarketing data. GAO stated that these problems "have prevented FDA from publishing statutorily required reports on certain potential safety issues and postmarketing studies in a timely manner, and have restricted the agency's ability to perform systematic oversight of postmarket drug safety." GAO concluded that "although FDA has taken some steps to address the problems with its data, it lacks comprehensive plans for doing so."

Although these study findings enlighten us on important issues, OIG, GAO, and Booz Allen studies examined postmarketing studies partially: BAH reviewed only postmarketing commitments before the 2007 FDAAA; OIG investigated only postmarketing requirements, not commitments; and GAO looked only at the postmarketing studies associated with expedited approvals. Also, the three-year follow-up of the BAH study leaves open the longer-term effects. In this paper, I will examine whether the patterns have changed in the last decade.

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<sup>36</sup> Fulfilled: 23%, Ongoing: 21%, Pending: 34%, Delayed: 7%, Released: 11%, Submitted: 4%, Terminated: 0.4%



Moreover, the BAH study looked only at agreed commitments between sponsors and FDA; the study excluded accelerated approvals and pediatric research requirements. Because it included only drugs approved prior to the 2007 FDAAA, the BAH study did not examine the difference between requirements and commitments in establishing and enforcing regulatory effects.

A few other studies have examined a smaller sample of drugs or postmarketing studies<sup>37</sup>. CSDD assessed 61 PMCs from 20 companies for 34 products (29 for FDA) approved during 1998-2005 in a 2007 study that was a survey of sponsors' views on postmarketing studies. Its research focused on the average length and cost of PMCs as well as drug sponsors' views on PMCs. Another study was conducted by Fan et al. (2016)<sup>38</sup> who looked at 40 PMR/PMCs for 35 NDAs in a specific type of postmarketing studies—membrane transporter related studies and found that 85% were considered fulfilled and 65% of them led to label changes. Although these studies provide insight on some part of the issues I will explain, their ability to generalize their finding to PMR/PMCs in other areas is weak.

The most recent study on postmarketing requirements was conducted by Wallach et al. (2018). They studied 437 PMRs for 97 new drugs and biologics approved between 2009 and 2012. They didn't include postmarketing commitments. The authors described PMRs by study design and characteristics and examined the results posted in clinicaltrials.gov database and publications in peer review journals. The major findings included:

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<sup>37</sup> Comparing these studies with the OIG and BAH studies is challenging. Study sample is different: OIG included only NDAs, but BAH included NDAs, BLAs, and supplements. BAH study did not include PREA, animal, and accelerated approval postmarketing requirements. OIG included only CDER drugs but BAH included both CDER and CBER drugs. Fan et al. searched open PMR/PMCs and CSDD depended on small number of firm survey.

<sup>38</sup> Only transporter-related PMR/PMC studies between January 1999 and May 2015. They searched the FDA database that contains open PMR/PMCs and PMR/PMCs that were fulfilled, released, or terminated within the last year.

- (1) Three quarters of PMRs for prospective cohort studies, registries, and clinical trials were registered on clinicaltrials.gov database (102 out of 134), and three quarters of completed studies reported results or were published (47 out of 65). Sixty-five of PMRs (15%) were completed.
- (2) Most of requirements were newly established studies (81%) – animal studies, other studies, clinical trials, registries, cohort studies, and observational studies. Eighty-three out of 437 requirements were for secondary analyses or follow-up studies (19%).
- (3) The majority of requirements reported public results after their original FDA report submission deadline. Of completed PMRs, the median time from approval to reported results or publication was 47 months.

Wallach et al. study (2018) makes relevant contributions, but looked at required studies over only four years. I look at all postmarketing studies established between July 2008 and May 2016 to capture the changes after the 2007 FDAAA.<sup>39</sup>

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<sup>39</sup> “On September 27, 2007, the President signed the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). Section 901, in Title IX of FDAAA, created section 505(o) of the Federal Food, Drug, and Cosmetic Act (the Act), which authorizes FDA to require certain studies and clinical trials for prescription drugs and biological products approved under section 505 of the Act or section 351 of the Public Health Service Act. This new authority became effective on March 25, 2008.”  
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm064633.htm>

**Table 1-3. Relevant Literature**

Study	Data Sample	Major Findings
Booz Allen, 2008	743 PMCs for all NDA, BLA, and supplemental approvals (CBER and CDER) between FY2002 and FY2005	Descriptive study on the establishment and characteristics of PMCs, types/categories/rationales for PMCs, and public health impact by examining label changes resulted from those PMCs.
CSDD, 2007	124 PMCs that had been submitted or fulfilled that were for NMEs and significant biologics approved between 1998 and 2005	45% were delayed due to enrollment problems, technical difficulties, needing to satisfy additional requirements, or by sponsors expanding the scope of their own studies. Clinical studies took 10 months longer than non-clinical studies. A majority of sponsors say studies contributed little to their understanding of the safety, efficacy, or quality of their product.
CSDD, 2008	29 NME or new biologic products that were approved between 1998 and 2008	The average number of postmarketing studies per new drug was 8.9. The number of PMCs varies by therapeutic area. Half of the products approved with PMCs had pediatric study requirements. The timing of agreements on PMCs is less consistent.
OIG, 2006	2,353 PMCs for new drug applications approved from FY1990 through FY2004	FDA cannot readily identify whether or how timely PMCs are progressing toward completion. Monitoring PMCs is not a top priority at FDA.
OIG, 2016	1,256 PMRs for NDA and supplemental approvals between FY2008 and FY2014	More PMRs were established for expedited approvals. Sponsors are completing PMRs although some are delayed. For about half of all fulfilled PMRs, FDA changed labels.
GAO, 2009	90 accelerated approvals from 1992 through November 20, 2008 and their confirmatory studies	FDA required 144 postmarketing confirmatory studies and as of Dec 2008, classified 64% as closed. Unlike surrogate endpoints used in the accelerated process, FDA does not require postmarketing confirmatory studies for NMEs approved on the basis of surrogate endpoints with traditional path. As of February 13, 2009, FDA classified about one-half as closed. Weaknesses in FDA's monitoring and enforcement process hamper its ability to effectively oversee postmarketing studies.

**Table 1 4. Relevant Literature (continued)**

Study	Data Sample	Major Findings
GAO, 2015	110 FT and BT approvals between Oct 2006 and Dec 2014 by CDER and CDER's internal evaluation of postmarket studies	FDA lacks reliable, readily accessible data on tracked safety issues and postmarketing studies needed to meet certain postmarket safety reporting responsibilities and to conduct systematic oversight although FDA has taken some steps.
Fan et al., 2016	40 transporter-related PMR/PMCs between Jan 1999 and May 2015	85% of them are considered “fulfilled” and 65% resulted in label changes. A significant lag time is anticipated between drug approval and PMR/PMC fulfillment.
Wallach et al., 2018	437 PMRs for new drugs and new biologics approved between 2009 and 2012	Descriptive study of PMR design, characteristics, rates and timeliness of registration and results reporting

### **1.3 Research questions, Methods, and Data**

#### **1.3.1 Research questions**

This paper describes the PMR/PMCs that were established between July 2008 and May 2016 (since the FDAAA of 2007). It explains when and how PMR/PMCs were established, what kinds of studies were required or requested, what they were expected to find, and whether they were carried out. As mentioned in Section 1.2.2, the Booz Allen and Hamilton report (2008) described FY2002-2005 postmarketing commitment cohort. This study will answer more nuanced questions for the 2008-2016 PMR/PMC sample.

First, I will review the trends of PMR/PMCs. Has the number of PMR/PMCs been increasing? Are more postmarketing studies getting established per drug? Are they getting longer

and larger as the pharma and bio industry claims<sup>40</sup>? Do we observe more clinical trials than literature reviews or additional analyses from existing trials? In what types of postmarketing studies or under what circumstances, do we observe such growth? These questions are meaningful for understanding the current state of PMR/PMCs with respect to the increasing cost and the value of postmarketing studies.

Second, this paper will look at the expedited approvals more closely. If speedy approvals create “the public concern about the safety implications,” as GAO states, more postmarketing studies, especially more PMRs, will be imposed on the expedited approvals (except for accelerated approvals<sup>41</sup>) compared to traditional approvals. Also, since the rationale for a FDAAA safety study is requiring a safety study so that it can be enforced, expedited approvals are expected to have higher percentage of FDAAA safety requirements compared to traditional approvals. And, we will examine whether expedited approvals are getting studied longer and in larger patient population after approval.

Lastly, this paper will inform us on how many postmarketing studies were fulfilled. Assessing the level of compliance addresses the policy issue of enforcement and management of PMR/PMCs the FDA faces today as stated in the section above. How many postmarketing studies are carried out? What are the reasons for delays?

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<sup>40</sup> “In the past, pharma companies looked to do postmarketing studies as quickly and cheaply as possible. But, late-phase trials are getting bigger, longer, more complicated, thus more expensive. As a result, pharma companies are looking for ways to use the data to create value for their organizations.....The biggest challenge is that regulatory bodies have been asking for increased patient numbers for any types of submission.....It used to be a five year study follow up was considered long. Now, it is nothing compared to 10-15 years of follow up required. Sponsors are challenged to come up with ways to get these studies done quickly and inexpensively. Sponsors are also challenged with how else they might use these data. Many sponsors are saying that FDA is asking for a 15-year study, and they are looking for other ways the data can be used to show value internally.” (Myshko, 2011)

<sup>41</sup> Drugs approved under the accelerated approval pathway need to be tested in clinical trials using endpoints that demonstrate clinical benefit, and those trials are known as confirmatory trials. If the confirmatory trials fail to prove clinical benefit, FDA may withdraw the drug approval. Because accelerated approvals are required to have postmarketing studies (PMRs), it makes sense to exclude accelerated approvals when looking at the association between expedited approvals and postmarketing studies.

### 1.3.2 Methods and Data

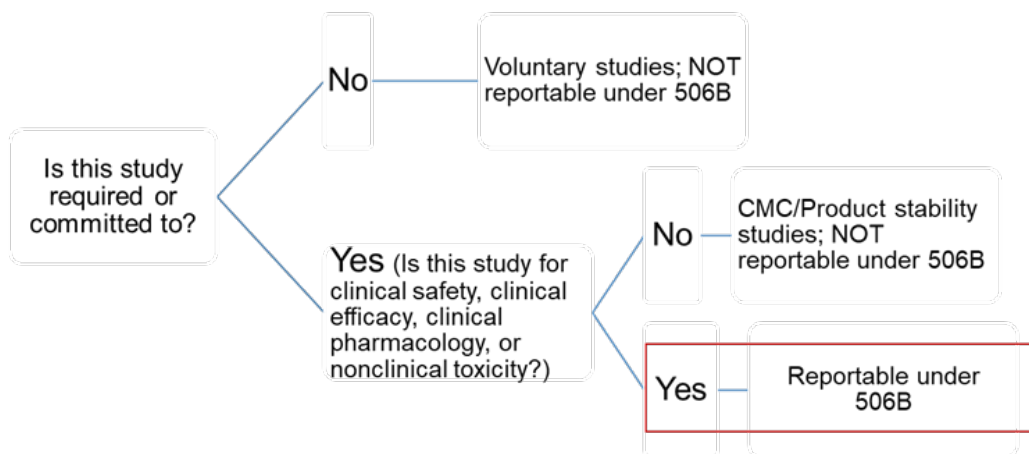
To answer the questions above, I analyzed the following datasets: (1) postmarketing studies that were established by CDER between July 1, 2008 and May 31, 2016 (for all new and supplemental approvals); (2) all new drug approvals (original NDA/BLAs) approved by CDER between July 1, 2008 and May 31, 2016; and (3) all NMEs approved by CDER between 1999 and 2017. FDA developed the current database for PMR/PMCs after the FDAAA of 2007, thus the FDA lacks complete data until June 2008.<sup>42</sup>

PMR/PMCs in this paper include only postmarketing studies and trials that are required by the FDA or agreed to the FDA and applicants. The reason for including only reportable studies is that the applicants are required to report the status of these PMR/PMCs under 506(B) section of FDCA<sup>43</sup>; and they would provide more relevant information about the questions proposed here. This means that I exclude non-reportable postmarketing studies for chemistry, manufacturing, and controls, product stability, and those voluntary studies that are neither required by FDA nor agreed upon between FDA and the applicant. (Figure 1-1)

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<sup>42</sup> From a phone conversation with CDER data management staff when requesting FOIA.

<sup>43</sup> Under 21 CFR 314.81(b)(2)(vii) and 601.70(a), the final rule defines postmarketing studies for which status reports must be submitted to FDA under section 506B of the act as those that concern: (1) Clinical safety; (2) clinical efficacy; (3) clinical pharmacology; and (4) nonclinical toxicology studies that are either required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or committed to by the applicant, in writing, at the time of approval of an application or a supplement or after approval of an application or supplement.



**Figure 1-1. Data Scope of this project**

Defining a “drug” can be tricky. A drug could be a drug product (with different forms and dosages), a brand name, or an active ingredient. A drug could have multiple NDA/BLA numbers and multiple drug products could share the same NDA/BLA number. And, a postmarketing study can be required for multiple NDA/BLAs. In this study, the meaningful units of analysis are “drug-approvals,” “approvals” and “postmarketing study.”

A drug-approval is a unique NDA/BLA number that is associated with a drug. An “approval” is a new or supplemental approval associated with a specific NDA/BLA number. A postmarketing study is a unique study that is associated with a specific approval. Postmarketing study ID was created by combining NDA/BLA number, original or supplement, supplemental approval sequence number, study type (FDAAA/AA/PREA/PMC), and study description.

A single drug or a single approval might have multiple PMR/PMCs. For example, as shown in Table 1-4, Cimzia (certolizumab pegol, a TNF inhibitor, BLA 125160 original) was approved in April 2008 with one PREA study and five FDAAA safety studies. In May 2009, a supplemental application (BLA 125160-S80) was approved with one PREA study and one FDAAA study. Another FDAAA study was added to the original approval in November 2011. Table 1-4 below

shows that a single drug and a single approval can have multiple PMR/PMCs and what a single PMR/PMC look like.

**Table 1-4. Example of PMR/PMCs: Cimzia**

Year	Approval	Study type	Study description
2008	Original	PREA	Conduct a study in pediatric patients, " <i>A Phase II Open-Label Multi-Center Study to Assess the Safety and Efficacy of Certolizumab pegol in Children and Adolescents with Active Crohn's Disease</i> " (Study CDP870-035). This study is proposed to evaluate the pharmacokinetics, safety and clinical response of pediatric patients, ages 6-17, with moderately to severely active Crohn's disease to treatment with CIMZIA <sup>TM</sup> .
2008	Original	FDAAA	A long-term observational study in the U.S. that will include approximately 2000 CIMZIA <sup>TM</sup> -treated Crohn's disease patients and 2000 matched controls receiving other treatments for Crohn's disease. Patients will be monitored for ten years.
2008	Original	FDAAA	CDP870-033, an ongoing open-label trial to assess the long-term safety of CIMZIA <sup>TM</sup> in patients with Crohn's disease who have previously completed trials CDP870-031 or CDP870-032. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA <sup>TM</sup> -treated patients. Patient follow-up will be extended to seven years from the start of treatment.
2008	Original	FDAAA	CDP870-034, an ongoing open-label trial to assess the long-term safety of re-exposure to CIMZIA <sup>TM</sup> after a variable interval in patients with Crohn's disease who were previously withdrawn from completed trials CDP870-031 or CDP870-032 due to an exacerbation of Crohn's disease. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA <sup>TM</sup> -treated patients. Patient follow-up will be extended to seven years from the start of treatment.
2008	Original	FDAAA	CDP870-088, an open-label trial to assess the long-term safety of CIMZIA <sup>TM</sup> in patients with Crohn's disease who have either completed trial CDP870-085 or were withdrawn from CDP870-085 due to an exacerbation of Crohn's disease. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA <sup>TM</sup> -treated patients. Patient follow-up will be extended to five years from the start of treatment.



**Table 1 5. Example of PMR/PMCs: Cimzia (continued)**

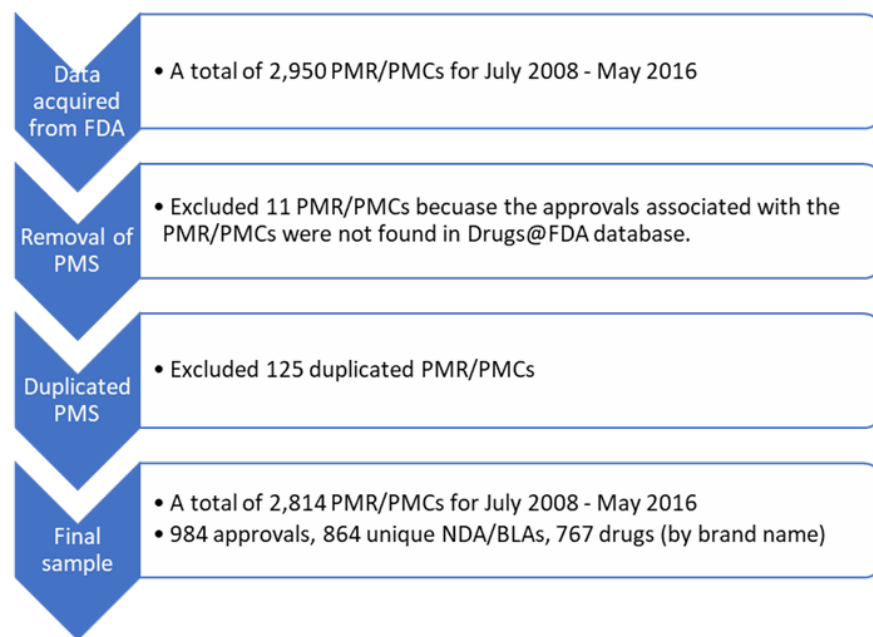
Year	Approval	Study type	Study description
2008	Original	FDAAA	A placebo-controlled trial designed to assess the effects of CIMZIA <sup>TM</sup> treatment on antibody responses to a B cell-mediated immunization, using pneumococcal vaccine immunization, and to a T cell-mediated immunization, using influenza vaccine, in patients with active rheumatoid arthritis. The study will measure both antibody titers and rates of clinical response in approximately 100 placebo- and 100 CIMZIA <sup>TM</sup> -treated patients who will be given polyvalent pneumococcal polysaccharide vaccine and influenza vaccine.
2009	Supplemental	PREA	Assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance and immunogenicity in the pediatric population 2 years to < 17 years with polyarticular JIA.
2009	Supplemental	FDAAA	An observational study registry in adult patients with moderately to severely active RA that would assess the longer-term risks of serious infections, malignancies that have been reported with TNF blocker therapy, as well as the longer term risk for cardiovascular and thromboembolic events, including congestive heart failure, hypertension, TIA, stroke, tachyarrhythmia, atrial fibrillation, venous thrombosis and phlebitis.
2011	Original	FDAAA	Enhanced pharmacovigilance program for reports of malignancy in pediatric, adolescent, and young adult (<30 years of age) patients treated with Cimzia (certolizumab pegol), for a period of up to 10 years after this notification to collect data that will be analyzed to better define the risk of this serious adverse event. The enhanced pharmacovigilance program includes the following: 1) active query of reporters to obtain additional clinical information related to malignancy diagnoses; 2) expedited reporting to FDA of all initial and follow-up reports of any malignancy in pediatric and young adult patients. Interim analyses and summaries of new and cumulative safety information in pediatric and young adult patients must be submitted annually, followed by the final report at the conclusion of the monitoring period.

[Source: FDA postmarketing requirements and commitments database]

Note: CDP870 is a drug code name which is often used before choosing a marketing name. The study codes (CDP870-031, CDP870-034, etc.) are defined by sponsors. FDA's postmarketing ID is a combination of a PMS set number and PMS number within the set. This ID is different from the study codes used by the companies.

I acquired two datasets (PMR/PMCs for July 2008 - July 2015 and PMR/PMCs for July 2015 - May 2016) for CDER-approved drugs via two FOIA requests. Merging the two datasets

created a list of 2,950 postmarketing studies. After deleting 125 duplicated PMR/PMCs<sup>44</sup>, I kept all other same PMR/PMCs for different NDA/BLAs. I also deleted 11 PMR/PMCs for drugs that have no information in Drugs@FDA database. This gives me a total of 2,814 PMR/PMCs for 984 approvals, 864 unique NDA/BLAs, or 767 unique drugs (by brand name). The average number of postmarketing studies established between July 2008 and May 2016 was 3.3 per new drug approval (original NDA/BLA) and 3.7 per drugs by brand name.



**Figure 1-2. Data Sample**

I linked the PMR/PMC dataset with FDA drug approval datasets as well as expedited approval datasets I created from FDA's public documents. In order to get data for the current

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<sup>44</sup> I excluded duplicated studies: there were duplicated entries because data for July 2015 was included in both datasets and because multiple supplemental drug approvals were granted at the same time with postmarketing studies (in this case, same PMR/PMCs were entered for each supplemental approval).

status<sup>45</sup> (pending, ongoing, delayed, submitted, released, terminated, and fulfilled) of PMR/PMCs, I linked the quarterly published PMR/PMC database that contains the status of PMR/PMC progress.

Also, this dataset of PMR/PMCs was linked with drug approval and expedited drug datasets in order to obtain drug information including:

- Approval date
- Current market status (discontinued, prescription)
- Approved chemical type
- Application type (NDA/BLA, supplement/original)
- Review class (priority, standard, orphan)
- Expedited approval paths (accelerated, fast track, and breakthrough)

To this dataset, several variables were added (see Table 1-18 in Appendix A for detailed coding rules and descriptions):

- Total number of PMR/PMCs, PMRs, and PMCs assigned to a drug
- Disease classes
- Establishment date
- Class action

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<sup>45</sup> FDA's postmarketing study dataset contains all descriptions and updates about "delays," but not all descriptions are available for other statuses of studies, i.e. "terminated," "released," etc. And, the status description overwrites when the status changes. For example, if a postmarketing study status has changed from delay missing milestone 1 (submitting protocol) to delay missing milestone 2 (complete patient recruitment), the current database contains description for missing milestone 2 because the new description overwrites the old description of delay on milestone 1. Thus, in some cases, it may be challenging to look at why studies are not carried out "on schedule." To complete this analysis, I compare progress statuses on quarterly updated downloadable files FDA posts on its website: I acquired files from July 2008 to October 2016 (open PMR/PMCs through October 31, 2016) via FOIA request and downloaded files myself from FDA's website.

- Study category, function, design, and sampling design
- Study purposes
- Study size and length

For disease classification, I employed WHO's ICD-10 codes<sup>46</sup> for the indications approved. ICD-10 codes provide 18 disease classes, but I simplified them into 14 categories by combining relevant categories. The disease classification rule is described in Tables 1-15 and 1-18 in Appendix A. The simplified therapeutic classes are: 1) Blood & Immune, 2) Cancer, 3) Circulatory, 4) Digestive, 5) Endocrine & Metabolism, 6) Imaging, 7) Infectious, 8) Musculoskeletal & Dermatology, 9) Pain & Anesthesia, 10) Parenteral Nutrition & Critical care, 11) Psychiatry & Neurology, 12) Reproductive, Urology, & Pregnancy, 13) Respiratory, and 14) Other.

Establishment date is the date the PMR/PMC was officially established by the FDA. Usually, it is the same as the approval date. But, sometimes, the FDA issues a separate letter of request for postmarketing studies and this information is not publicly available. For PMR/PMCs without establishment date information, I coded approval date as establishment date when approval letters were available. For PMR/PMC class actions, I coded the establishment date as stated in the

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<sup>46</sup> WHO's ICD-10 classification provides 18 disease classes: Certain infectious and parasitic diseases, Neoplasms, Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, Endocrine, nutritional and metabolic diseases, Mental, Behavioral and Neurodevelopmental disorders, Diseases of the nervous system, Diseases of the eye and adnexa, Diseases of the ear and mastoid process, Diseases of the circulatory system, Diseases of the respiratory system, Diseases of the digestive system, Diseases of the skin and subcutaneous tissue, Diseases of the musculoskeletal system and connective tissue, Diseases of the genitourinary system, Pregnancy, childbirth and the puerperium, Certain conditions originating in the perinatal period, Congenital malformations, deformations and chromosomal abnormalities, and Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified.

FDA’s communication on the website for class-wide PMR/PMCs (i.e. opioid postmarketing safety requirements).

For the PMR/PMCs that had neither approval letters nor class action dates, I used FDA’s quarterly published datasets to find when a postmarketing study first appear in the datasets. For example, the FDA established a QT<sup>47</sup> postmarketing study for Efavirenz (HIV drug) that was approved in 1998. Since the PMR/PMC was associated with its original approval in 1998, I looked at all supplemental approvals since 1998 but failed to find the safety study anywhere. Thus, I searched the quarterly database and found the study first appeared in the second quarter dataset in 2014.<sup>48</sup> The second quarter data contains PMR/PMCs for February 1 – April 30, and I coded the establishment date as March 15 which is the middle point.

I define “class action” as FDA’s establishing the same PMR/PMCs for multiple drugs in the same class due to safety concerns. FDA communicates and announces safety information not only about individual drugs but drug classes<sup>49</sup>. For this task, I used a postmarketing set number that was acquired through FOIA request. Set number is the number of the set to which the PMR/PMC belongs. In most cases, postmarketing studies associated with an approval belong to one set number. Or, the same postmarketing studies established for all drugs in a class belong to one set number and this is what I define a “class action.” For instance, the FDA established 80 postmarketing studies for all opioid drugs available in the market in 2013-2014 and then it replaced the class-wide PMRs with more postmarketing studies for all opioids in 2016. This is an action for all drugs in a class.

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<sup>47</sup> QT is a measurement, made from the electrocardiogram (ECG or EKG). It reflects the duration of the electrical activity that controls contraction of the cells of the heart muscle.

<sup>48</sup> Quarterly dataset is updated usually late. Not rarely I find a study appears 3-6 months later the study was established (approval letter).

<sup>49</sup> <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/default.htm>

**Table 1-5. PMR/PMC classification by study newness, function, design, and purpose**

Newness	Function	Design	Purpose
New Ongoing/existing Sub-study Follow-up Undetermined	Conduct Submit report/data Develop/validate Undetermined	Analysis Chemistry Observational Nonclinical toxicology In-Vitro/In-Vivo/Ex-vivo Trial follow-up Trial (RCT, non-R, unspecified) Pooled analysis Other Undetermined	Biopharmaceutics Confirmatory Drug-Drug Interaction Dose Efficacy Safety Immunogenicity Microbiology Multipurpose Other Other - Pharmacology Utilization Product Undetermined

Notes: Not all combinations of the four categories (newness, function, design, and purpose) are observable. For example, submitting report/data is only for ongoing/existing studies, sub-studies, or follow-ups. And, developing/validating methods or measures and chemistry/product analysis studies are all new studies.

In order to investigate study characteristics, I created the following variables (See Table 1-16 and Table 1-18 in Appendix A): study category, study design, and study purpose. Study categories are classified by two measures. The first is the newness of studies: whether the study is a new study, ongoing/existing study, sub-study, or follow-up. A new study is a study that is newly established without association with existing studies. An ongoing/existing study is a study that is ongoing (at least protocol established) or already done. A sub-study is a study established under existing studies. A follow-up is a follow-up study of subjects enrolled in existing trials.

The second measure is the function of studies: conduct, develop/validate method, or submit (report or data). “Conduct” is conducting a study that is new, follow-up, ongoing/existing, or sub-study. “Develop/validate” means developing or validating methods or measures. Some requirements and commitments are simply about submitting the final reports or data, and in this case, the function of the study is defined as “submit.”

Combining the two measures, I classified PMR/PMCs into 7 categories depending on the nature of the studies: conducting new study, conducting follow-up, conducting sub-study,

conducting ongoing/existing study, submitting report/data for ongoing/existing study, submitting report/data for follow-up, and developing or validating method or measure.

In addition, study design was coded based on study descriptions.<sup>50</sup> Clinical trials were classified by randomization when information was available. When such information was not available, I coded them as “trial, unspecified.” Observational studies are studies where the investigator didn’t give an intervention to the subjects and nonclinical toxicology studies are animal toxicology studies. And, analysis studies are an analysis or re-analysis of data from trials, observational, or spontaneous reports. Pooled analyses are studies that require analysis of data from multiple studies to infer certain outcomes. Trial follow-ups are follow-up studies of clinical trials, and chemistry studies are impurity/individual component studies. Only in-vivo animal models were included in the in-vitro, in-vivo, and ex-vivo study category: in-vivo trials were classified as clinical trials. Other study design includes banking samples, feasibility studies, collecting data (not including analysis), convening panel experts, developing and validating methods/measures/algorithm, expanding registries, and publishing academic paper.

Furthermore, study purpose was coded based on the study descriptions. Purposes of dose, clinical efficacy, clinical safety, and drug-drug interaction (DDI) studies are self-explanatory. Confirmatory studies are to confirm clinical benefits, and requirements for accelerated approvals and animal rule approvals belong to this group. Immunogenicity studies include anti-drug antibody studies, antigen processing, developing and validating method to study immunogenicity.

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<sup>50</sup> Note that study design is not specified for many PREA studies. Typical PREA studies look like “Deferred pediatric study under PREA to assess the pharmacokinetics, safety, and tolerability in pediatric patients 6 to 16 years of age with minor soft tissue injuries” or “A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17 years. A study of the efficacy and safety of asenapine sublingual tablets in the relevant pediatric population.” Furthermore, many studies have multipurpose – the nature of PREA studies is to seek approval for a new indication for pediatric population. Therefore, FDA asks sponsors to present PK, safety, and efficacy data to determine the appropriate dose, safety, and efficacy of the drug – these are usually phase I and II trials but sometimes phase III trials are included.

Microbiology studies are to examine susceptibility, drug resistance, phenotype/genotype analyses, substitution, or virologic failure. Biopharmaceutic studies aim to investigate bioavailability, bioequivalence, and food effect studies. Drug utilization studies include developing and validating measures/codes for misuse, abuse, addiction, and overdose, general drug utilization studies, epidemiologic studies on misuse and abuse, etc. Studies on the product quality and control studies such as product impurity, product stability, batch test, etc. as well as developing methods for determining individual component were classified as “product” related studies. Other-pharmacology studies include PK/PD general studies, exposure-response, biomarkers, ADME (absorption, distinction, metabolism, and excretion), and mass balance studies. All other studies such as administration method, withdrawal, dose equivalence, assay development, dependence, etc. were classified as “other” study purpose.

Finally, I coded the length and size of studies based on study descriptions from FDA PMR/PMC database and clinicaltrials.gov database using NCT number (clinical trial registry number) whenever available. I looked up “study start date,” “primary completion date,” and/or “study completion date” in the registry database. Study start date is “the actual date on which the first participant was enrolled in a clinical study.” Primary completion date is “the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure.” And, study completion date is “the date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit).”<sup>51</sup> I used the primary completion date for the ongoing/existing trials

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<sup>51</sup> Definitions of study start date and primary completion date can be found on clinicaltrials.gov.



and the study completion date for the follow-up/observational/analysis studies. I also coded the actual enrollment as the number of participants in a clinical study.<sup>52</sup>

## **1.4 Findings**

### **1.4.1 Overview of PMR/PMCs**

Table 1-6 below shows an overview of all postmarketing studies established by CDER during July 1, 2008 – May 31, 2016. This dataset contains all new and supplemental NDA/BLAs associated with the PMR/PMCs established during that period. A total of 2,814 postmarketing studies were established and, on average, 343 studies were established yearly (CY 2009-2015). Those 2,814 studies are associated with 767 drugs, 864 NDA/BLAs, or 984 new and supplemental approvals.

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<sup>52</sup> However, the length/size of a study stated on the study description and actual length and size of study may differ (usually the data from study descriptions were underestimated). For example, a study on Nucala (BLA #125526) was described as “Conduct a 12-month long-term safety and pharmacodynamics extension study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part B of Study 200363).” By description, the study length was 12 months. But, the actual length of study in the registry was 16 months. In order to secure consistency and more sample size (new studies usually don’t have the NCT number – not yet registered.), I included the actual length and size for the ongoing/existing trials (primary completion date) or follow-up/observational/analysis studies (study completion date).

**Table 1-6. PMR/PMCs by type, July 2008 – May 2016**

Postmarketing studies Flag		Drug application type		Drug type		Total
		New	Supplemental	NDA	BLA	
Requirements (PMR)	Accelerated	64	24	73	15	88
	Animal	3	11	9	5	14
	PREA	621	152	726	47	773
	FDAAA	1,394	157	1,359	192	<b>1,551</b>
	PMR Total	2,082	344	2,167	259	<b>2,426</b>
Commitments (PMC)		273	115	267	121	388
TOTAL		2,355	459	2,434	380	<b>2,814</b>

[Acronyms] PREA: Pediatric Research Equity Act; FDAAA: Food and Drug Administration Amendments Act; NDA: New Drug Application; BLA: Biologic License Application

As Table 1-6 shows, the majority of postmarketing studies were established for new drugs (especially NMEs) and NDAs (see also Tables 1-12 and 1-13 in Appendix A). However, the number of PMR/PMCS for new drugs is overestimated because 418 PMR/PMCs were established for approvals that were granted before 2008 (from 1947 to 2007) – the vast majority of approvals are original approvals (409 out of 418).<sup>53</sup>

As Table 1-6 shows, FDAAA safety requirements make up 55% of all postmarketing requirements and commitments. Only 14% of postmarketing studies are commitments. Although not shown in the text<sup>54</sup>, among new drugs NMEs are much more likely to have postmarketing studies compared to other chemical types (84% of NMEs approved during July 2008 – May 2016 had postmarketing studies, and on average 5.3 studies). It is not surprising because NMEs are considered an ingredient “never approved by FDA” and thus more uncertainty is perceived for NMEs.

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<sup>53</sup> For example, dolophine hydrochloride, a pain medicine, was approved in 1947. As a part of a class action (see section 1.4.3 for details) in 2016, FDA required FDAAA safety studies that address opioid addiction, abuse, and misuse and FDA associated these studies with the original approval granted in 1947. Therefore, these studies are not actually associated with “new drugs” but they are counted as postmarketing studies for “new drug” because the associated approvals are original approvals.

<sup>54</sup> See Figure 1-18 in Appendix B for the percentage of NMEs and non-NMEs with postmarketing studies yearly.

### 1.4.2 Trends in the use of PMR/PMCs

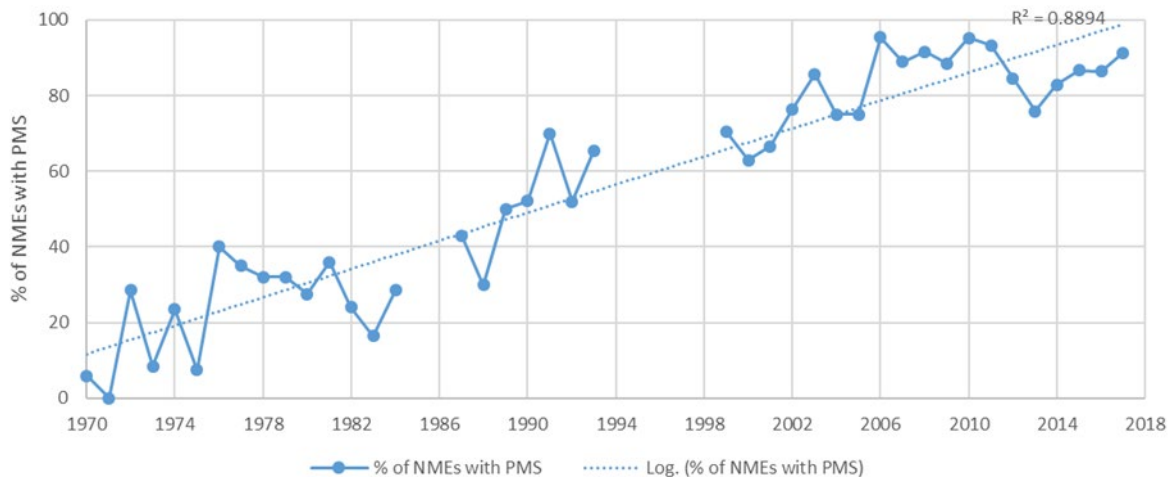
Since the 1970s, more drugs have been approved with postmarketing requirements and/or commitments. Figure 1-3 below exhibits the percentage of NMEs<sup>55</sup> with at least one postmarketing study over time since 1970. Despite some fluctuations, it clearly shows an upward trend: more NMEs are approved with at least one postmarketing study. Between 1970 and 1975, the percentage of new chemical entities (NCEs)<sup>56</sup> with a postmarketing study averaged 12%. Since 2008, on average, 87% of NMEs have been approved with at least one postmarketing study.

Figure 1-3 shows that, subsequent to FDAAA in 2007, the percentage of NMEs with any PMR/PMC stabilized and then dropped through 2013, when it began to increase again. Figure 1-4 shows the same measure for a broader group of drugs: the percentage of all NDAs with at least one PMR/PMC is still higher in 2008-2016 than in 1990-2004, but the increasing trend is flatter than for NMEs. Here we also observe a decline in the percentage after FDAAA, but we don't see the same upturn since 2013.

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<sup>55</sup> An NME is a drug that contains an active moiety that has never been approved by the FDA or marketed in the U.S. The term NME is not defined in the statute or regulations.

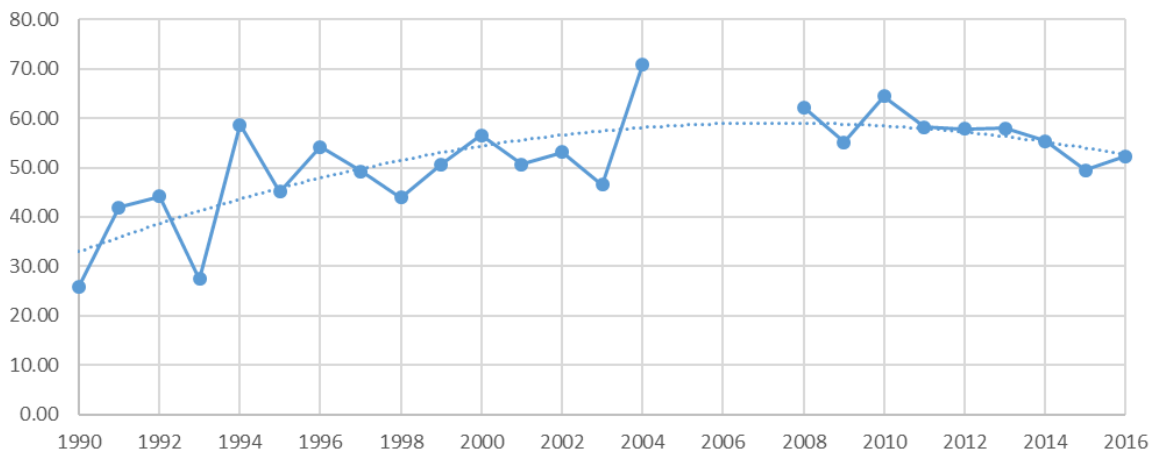
<sup>56</sup> An NCE is a drug that contains no active moiety that has been approved by FDA in any other application submitted under FDC Act § 505(b). FDA's classification of a drug as an NME for review purposes is distinct from FDA's determination of whether a drug product is an NCE within the meaning of the FD&C Act. Although their definitions are different, they are very similar in terms of characteristic of "newness."



**Figure 1-3. Time trend: Percentage of NMEs with at least one PMR/PMC (1970-2017)**

Notes:

1. No dataset is available for NMEs with PMR/PMCs over an extended period of time, and therefore this graph was derived from three different data source: (1) Mattison and Richard data (NCEs approved during 1970-1984), (2) OIG data (NMEs approved during 1987-1993), and (3) author's own data (NMEs approved during 1999-2017). The trend line for % of NMEs with postmarketing studies is logarithmic:  $y = 3698.6 \ln(x) - 28045$ ,  $R^2 = 0.8894$
2. No data on the number of PMR/PMCs (the number of PMR/PMCs for approved NMEs) is available before 2008 except the 1996 OIG data (1987-1993). There is no obvious trend in the number of PMR/PMCs.
3. Total number of NMEs for 1987-1993: 169, total number of NMEs for 1999-2017: 542

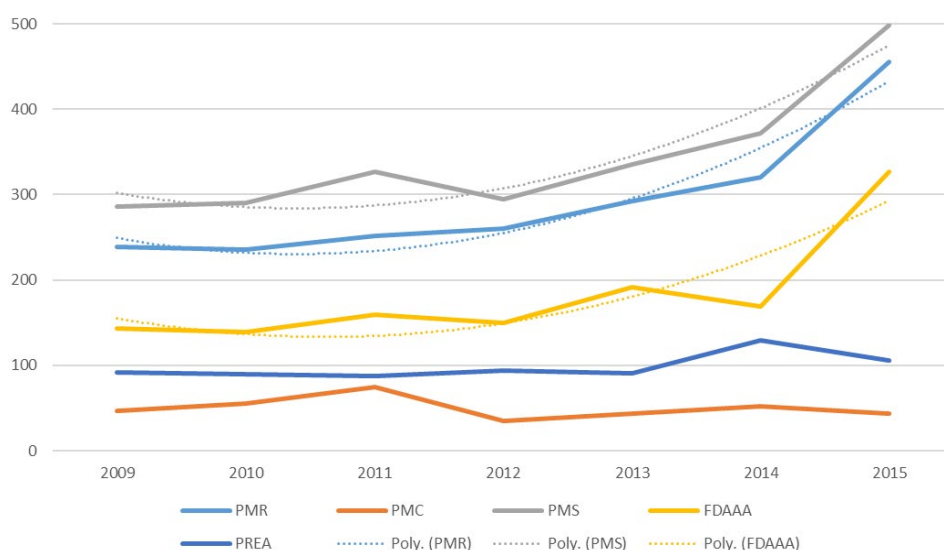


**Figure 1-4. The percentage of new drug applications (NDAs) with at least one PMR/PMC (1990-2016)**

Notes:

1. Source: data for 1990-2004 (fiscal year) come from OIG report (2006) and data for 2008-2016 (calendar year) come from author's own analysis.
2. This graph contains new drug applications (NDAs) approved by CDER because the 2006 OIG report didn't include BLAs.

Let us turn to looking at the number of postmarketing studies per original NDA/BLA approved by CDER. Figure 1-5 presents the trends in the number of postmarketing studies between 2009 and 2015. It shows there is an upward trend in the number of postmarketing studies after 2012, an increase limited to PMRs, especially FDAAA safety requirements. Again, this dataset is different from the datasets used for Figures 1-3 and 1-4. As shown in those figures, for NMEs and new drugs approved 2008-2016, there was no clear evidence for increasing number of new drug approvals with PMR/PMCs since the FDAAA. But, when including all PMR/PMCs established, an increasing trend in the number of PMR/PMCs is observed.



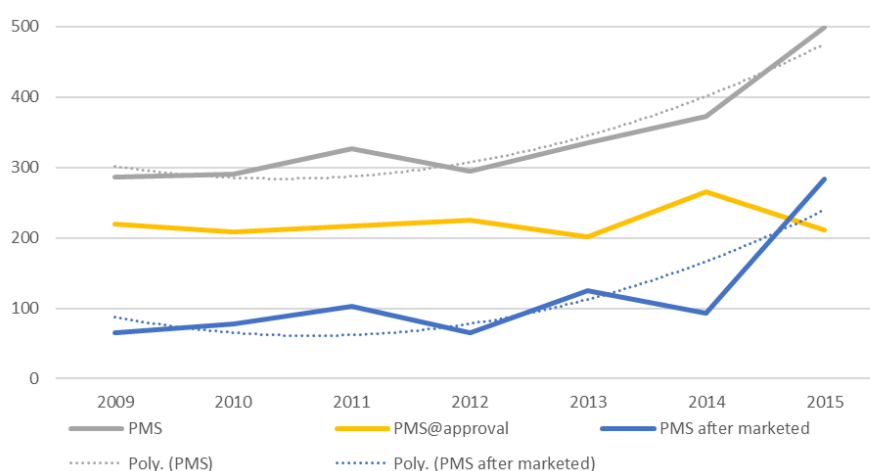
**Figure 1-5. Number of PMR/PMCs established 2009-20**

Notes:

1. PMR/PMCs established in 2008 (Jul – Dec 2008) and 2016 (Jan – May) were excluded from analysis.
2. Poly lines refer to polynomial trendlines that are curved lines using polynomial equations to calculate the least squares fit through points.

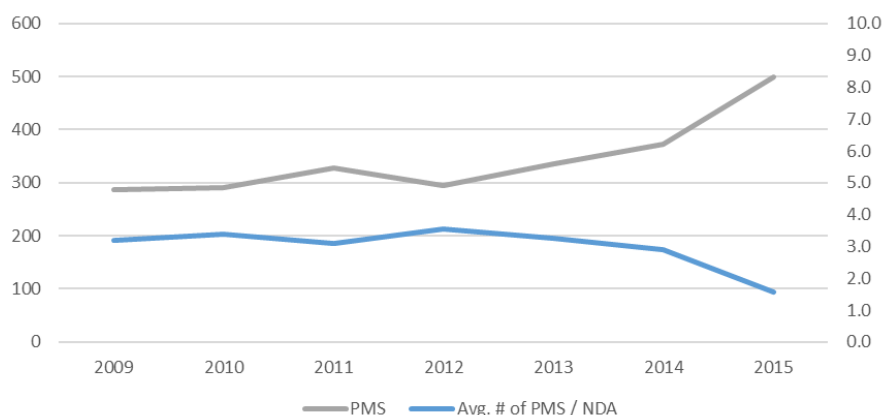
This upward trend can be attributed to the increasing number of PMR/PMCs for drugs that were already marketed and/or increasing number of PMR/PMCs per drug approval. Figure 1-6 shows that the number of PMR/PMCs established for already marketed drugs has increased while

no such trend in the number of postmarketing studies for new drug approvals since 2008. Figure 1-7 shows that the average number of PMR/PMCs per drug approval has decreased while the total number of PMR/PMCs has increased. These two figures imply that the increase in the total number of established PMR/PMCs is attributed to the increase in the number of drug approvals that have PMR/PMCs subsequent to marketing rather than the average number of PMR/PMCs per drug approval.



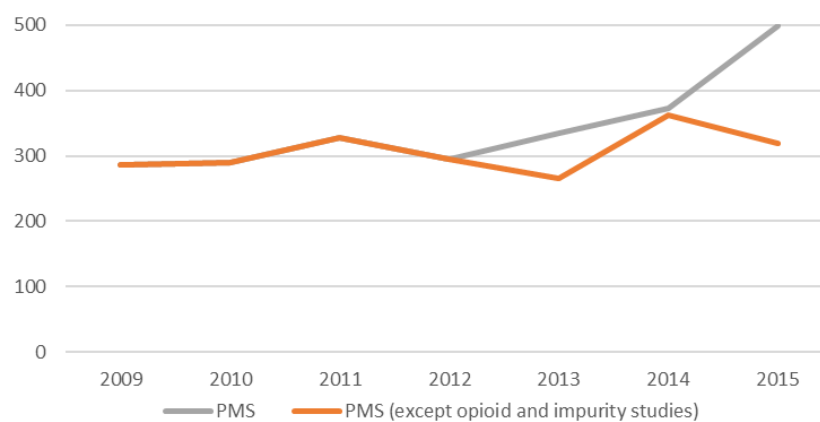
**Figure 1-6. Number of PMR/PMCs, 2009-2015, by the timing of PMR/PMCs**

Note: The yellow line shows the number of postmarketing studies that were established at the time of approval.



**Figure 1-7. Total number of PMR/PMCs and average number of PMR/PMCs per drug approval, 2009-2015**

On the other hand, Figure 1-8 shows that the upward trend in the total number of PMR/PMCs can be explained by some class actions. When excluding two large class actions (256 safety studies on opioid drugs and 180 chemistry/impurity studies on parenteral nutrition/critical care drugs), there is no apparent increasing trend in the number of studies. See Section 1.4.3 for class actions.



**Figure 1-8. Total number of PMR/PMCs and number of PMR/PMCs without two most outstanding class actions**

Notes: the grey line is the total number of PMR/PMCs by year and the orange line is the total number of PMR/PMCs except for two large class actions—opioid studies and impurity studies for parental/nutrition/critical care drugs.

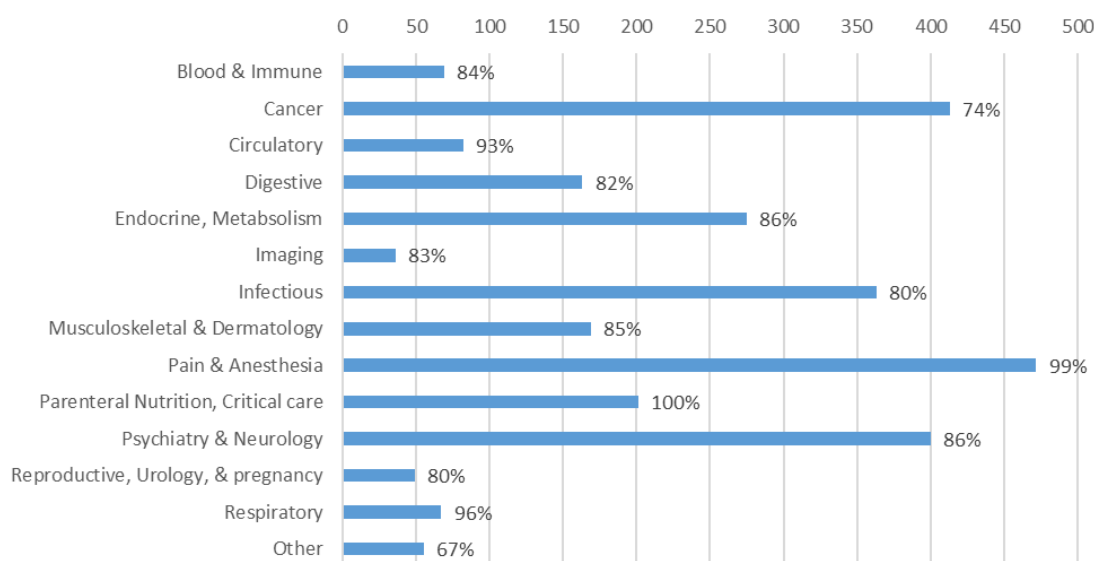
Compared to the BAH study (all approvals with PMCs between fiscal year 2002-2005), the total number of postmarketing studies has slightly increased since 2005. Because Booz Allen did not include required studies for accelerated approvals, animal approvals, and pediatric studies, our comparison is limited to FDAAA safety studies and PMCs in the current dataset with the postmarketing studies included in the BAH study. The average number of FDAAA studies and postmarketing commitments per year has increased to 233 (2009-2015) from 216 (2002-2005).

In summary, the number of postmarketing studies have increased since 2009 and compared to the time period of 2002-2005. We learned that the increase is attributable to the increase in the PMR/PMCs for already marketed drugs. And, this growth is likely to have been driven by class actions.

### **1.4.3 Disease classes and Class actions**

In this section, I examine postmarketing studies by disease-therapeutic class. Drugs in pain and anesthesia had the highest number of postmarketing studies followed by cancer, psychiatry, nervous system disease and infectious disease (Figure 1-9). Almost all postmarketing studies in pain and anesthesia were requirements (99%). This was a response to the opioid epidemic that had become a public concern. For cancer drugs, 74% of studies were required; for infectious disease, 80%; and for nervous system diseases, 86%. Seventy four percent of confirmatory trials for accelerated approvals were for cancer drugs. Most of animal studies were for infectious diseases (86%) [Table 1-16 in Appendix A].





**Figure 1-9. Total number of PMR/PMCs and the percentage of PMRs of total PMR/PMCs, by disease class**

Note: the percentage represents the percentage of postmarketing requirements out of total postmarketing studies

The three largest numbers of FDAAA studies, by disease category, were 350 (pain & anesthesia), 239 (cancer), and 196 (parenteral nutrition, critical care). The percentage of FDAAA safety studies out of all postmarketing studies was the largest in parenteral nutrition & critical care (98%) and pain & anesthesia (74%). The smallest percentage of FDAAA safety studies was observed in respiratory drugs (18%) and digestive drugs (32%)—those two disease-drug classes have higher ratio of PREA studies instead (78% PREA studies in respiratory drugs and 49% PREA studies in digestive drugs). See Table 1-16 in Appendix A for further details.

Let us compare the average number of postmarketing studies per drug approval by disease class. The three largest numbers of PMR/PMCs per drug approval were 6.1 (pain and anesthesia), 4.9 (cancer), and 4.0 (digestive). And, the three smallest numbers of PMR/PMCs per drug approval were 1.1 (parenteral nutrition, critical care), 1.3 (imaging), and 2.1 (reproductive, urology, and pregnancy). See Table 1-17 in Appendix A.

The FDA usually decides whether to require postmarketing studies and, if so, what kinds, at the time of approval. This information is included in the approval letter. But another way of establishing PMR/PMCs is a class action. For example, many postmarketing studies for pain drugs were established through a class action on opioid drugs. (Table 1-7)

**Table 1-7. Major class actions, FDAAA safety studies**

Drug class	PMR set year	# of PMR	# of approvals	Contents
Opioid	2013-2014	80	16	Risks of misuse, abuse, addiction, overdose, and death associated with long-term use, risk for the development of hyperalgesia, doctor/pharmacy shopping
	2016	176	16	Observational study on opioid misuse and abuse and doctor/pharmacy shopping, Trial on serious risk for the development of hyperalgesia, etc.
Parenteral Nutrition, Critical care	2015	180	180	Impurity studies, contamination test: test and control for lead, arsenic, cadmium, mercury, chromium, copper, selenium, manganese, zinc and metals
Imaging, MR, Contrast	2015	17	17	An observational study of pediatric patients from birth to 3 years to assess their risk of developing hypothyroidism.
	2007-2010*	13	13	A clinical trial to assess the magnitude of risk for the development of NSF

\*: FDA established some of the PMRs in September 2007, but in the FDA PMR/PMC database, they were established after July 2008. In the quarterly datasets, these studies first appear on the first quarter of 2010. I marked 2010 as an establishment date for these studies.

In September 2013, FDA announced “a set of significant measures to enhance the safe and appropriate use of extended-release and long-acting (ER/LA) opioids, including class-wide safety labeling changes and new post-marketing requirements for all ER/LA opioid analgesics.”<sup>57</sup> In February 2016, FDA released the previous 5 PMRs and replaced them with 11 PMRs (10 studies and one clinical trial) because the 10 observational studies and one clinical trial “include refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose, and death.”<sup>58</sup>

<sup>57</sup> <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm>

<sup>58</sup> <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm>

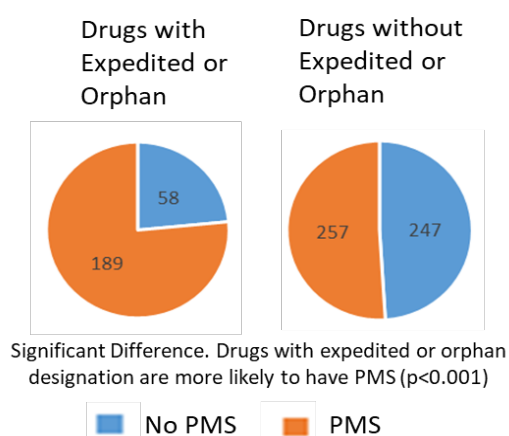
All such class actions call for FDAAA safety requirements. Although major class actions do not occur often, it increases the number of postmarketing studies significantly because of the large number of drugs affected by the class actions. These class actions resulted in 256 PMRs for opioid medications, 180 PMRs for parenteral nutrition and critical care products, and 30 PMRs for contrast media products. Considering 250-300 postmarketing studies had been established yearly during 2009-2012, these class actions explain large part of postmarketing studies in 2014 and 2015. The total number of postmarketing studies established each year has been steady during 2009-2012 and rose during 2013-2015.

#### **1.4.4 Expedited approvals**

In this section, I examine whether expedited approvals are more likely to have postmarketing studies. The widely-accepted view is that expedited approvals are riskier than traditional approvals. The underlying assumption is that expedited approvals are deemed to have the greater potential for treatment and greater benefit and thus reviewers take it into account when determining approval and whether an issue can be resolved in the post-approval settings. Thus, higher percentage of drug approvals with postmarketing studies for expedited approvals and more postmarketing studies per expedited drug approval are expected. The same case can be made for orphan drugs because orphan drugs address unmet medical needs (and thus potential benefit is assumed).

Figure 1-10 shows the number of new drug approvals with PMR/PMCs and without PMR/PMCs by expedited approval path designation and orphan drug designation. Accelerated approvals were excluded from the analysis because confirmatory trials are legally mandated for accelerated approvals. A sample of 753 new drug approvals by CDER between July 2008 and May

2016 was examined (2 drug approvals were excluded from the analysis due to data availability). The expedited approval paths here include breakthrough therapy, priority review, and fast track; orphan designation is also included. These are paths designated to drugs that 1) demonstrate improvement over available therapy; 2) improvement in safety and efficacy; and/or 3) address serious diseases and unmet medical needs. As shown in Figure 1-10, drugs with expedited approval or orphan designation are more likely to be approved with PMR/PMCs than drugs without any of the designations. See Figure 1-25 in Appendix B for further breakdowns.



**Figure 1-10. The number of new drug approvals with and without PMR/PMCs, by expedited or orphan designation**

Notes:

1. 751 new NDA/BLAs approved between July 2008 and May 2016 (2 approvals were excluded due to data availability)
2. The numbers within the pie charts indicate the number of NDA/BLAs.
3. Accelerated approvals were excluded from the analysis because PMR is mandated when accelerated approvals are granted.
4. See Figure 1-25 in Appendix B for breakdowns of each expedited path and orphan designation.

Figure 1-10 showed that expedited approvals had more postmarketing studies than traditional approvals. On average, an expedited approval had 4.3 PMR/PMCs while a traditional

approval (non-expedited) had 3.2.<sup>59</sup> When looking at Table 1-8, it seems clearer: the more expedited pathways designated to a drug, the greater number of postmarketing studies. Among expedited approval pathways, fast track and breakthrough drugs were approved with many more PMR/PMCs.

**Table 1-8. Number of postmarketing studies by study type and number of expedited pathways designated for approvals**

Number of expedited pathways	Postmarketing Requirement Type				Postmarketing Study			Approvals	Average PMR/PMCs
	Accelerated	Animal	FDAAA	PREA	PMR subtotal	PMC	TOTAL		
0 (traditional)	-	-	595	548	1,143	121	1,264	401	3.2
1	13	3	339	82	437	76	513	129	4.0
2	27	2	171	46	246	93	339	75	4.5
3	27	-	67	6	100	34	134	27	5.0
4	6	-	10	-	16	3	19	3	6.3
n/a	15	9	369	91	484	61	545	349	1.6
Expedited_total	73	5	587	134	799	206	1,005	234	4.3
Total	88	14	1,551	773	2,426	388	2,814	984	2.9

Notes: When excluding accelerated approvals, the average PMR/PMCs per approval is 3.1 for traditional approval, 4.0 for approvals with 1 expedited path, 4.7 for approvals with 2 expedited paths, and 6.1 for approvals with 3 expedited paths. Sample size: 2,574 PMR/PMCs and 923 approvals.

As Table 1-8 shows, for FDAAA safety studies, when considering the number of drug approvals, expedited drug approvals had 2.5 studies on average while traditional drug approvals had only 1.5 studies on average. Also, the average number of postmarketing requirements per approval was higher for expedited approvals (3.4) compared to traditional approvals (2.9), but not substantially. It is because many PMRs for traditional approvals are pediatric requirements (48%).

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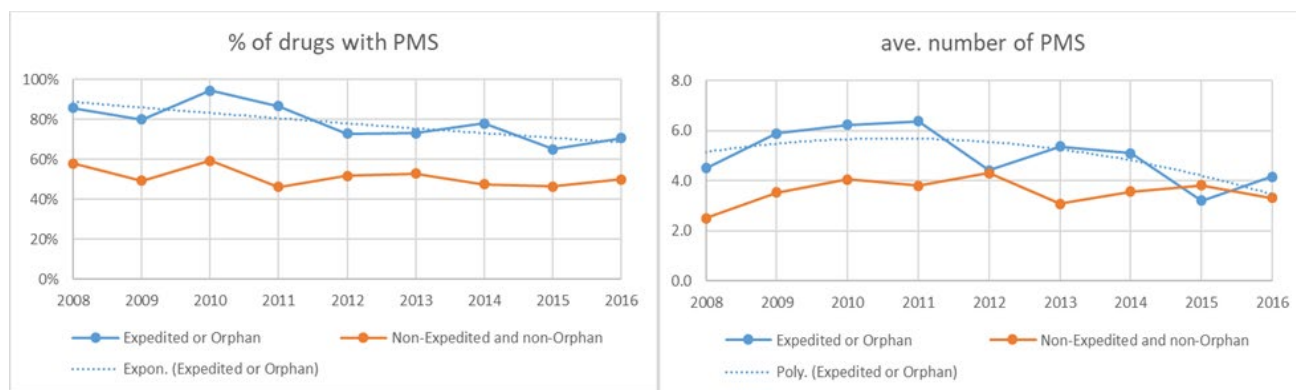
<sup>59</sup> In the dataset of 984 approvals for 2,814 PMR/PMCs, 87 approvals were undetermined for the expedited programs. A total of 897 drug approvals with information on expedited approval path were associated with 2,644 PMR/PMCs. Out of 897 approvals, 292 approvals (45%) had one or more expedited programs. This makes 42% of postmarketing studies associated with approvals had one or more expedited approval path(s).

Often, drugs approved with expedited pathways get pediatric studies waived because orphan drugs are exempt from PREA (many orphan drugs are expedited) and sometimes a drug is contraindicated for pediatric groups when highly toxic. After excluding PREA, 665 PMRs were established for 234 expedited approvals (2.8 on average) and 595 PMRs were established for 401 traditional approvals (1.5 on average).

To look at the trends in the percentage of new drug approvals with PMR/PMCs and the average number of PMR/PMCs per drug over time, I examined 749 out of 753 CDER's new drug approvals between July 2008 and May 2016 (the expedited status for 4 drug approvals were unknown). Figure 1-11 shows the trends in the percentage of drug approvals with postmarketing studies and the average number of PMR/PMCs per approval for drugs with expedited or orphan designation and drugs without such designation. We observe no trends in traditional approvals (non-expedited and non-orphan). For expedited or orphan drugs, we observe slight declines in both the percentage of approvals with postmarketing studies and the average number of postmarketing studies per approval.<sup>60</sup>

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<sup>60</sup> The priority review (if significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications) is designated to drug approvals more generously than fast track or breakthrough therapy. Thus, for expedited drugs, the decreasing trend may not be the same when the priority review was excluded. In order to see any possible difference, Figure 1-24 in Appendix B shows the average number of postmarketing studies for expedited or orphan drugs without priority review designation. Without priority review, the average number of postmarketing studies for expedited or orphan drugs is decreasing over time and no obvious trend on the average number of postmarketing studies for traditional drugs was observed.



**Figure 1-11. The percentage of drug approvals with PMR/PMCs and average number of PMR/PMCs per approval, by expedited\_orphan status and year**

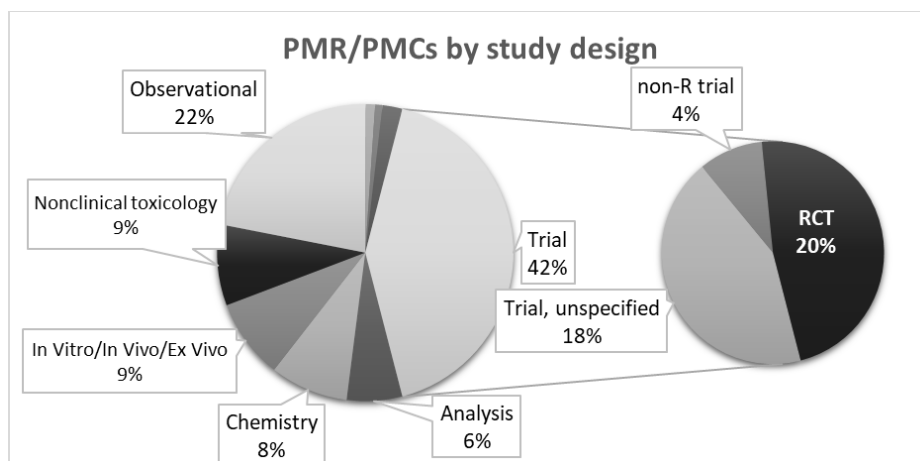
Note: The figures show the percentage of drug approvals with PMR/PMCs and the average number of PMR/PMCs per drug approval, respectively, for expedited or orphan drugs and non-expedited-nor-orphan drugs.

### 1.4.5 Designs and purposes of studies

For descriptions on types of postmarketing studies, see Appendix C.

#### Study Design

Figure 1-12 presents a snapshot of PMR/PMCs by study design. Among 2,269 studies whose study design was determined, 42% were clinical trials, 22% were observational studies and nonclinical toxicology studies were 9% as were in-vitro/in-vivo/ex-vivo studies. Among clinical trials, 47% was randomized, 9% was non-randomized, and randomization was undetermined for 43%.



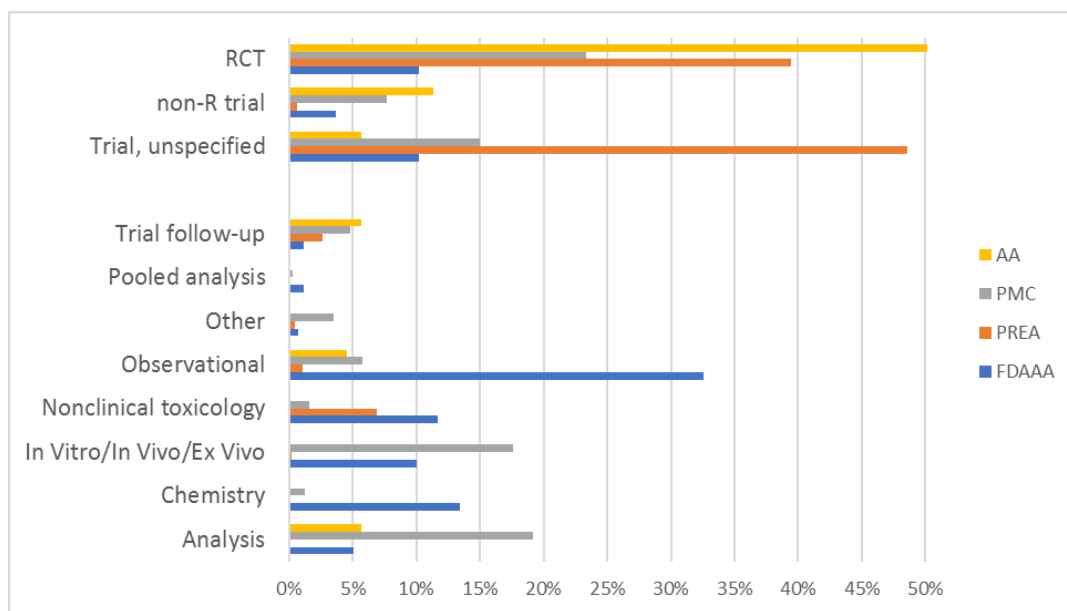
**Figure 1-12. PMR/PMCs by study design**

**Notes:**

1. Chemistry studies – impurity studies or individual component analysis in batches
2. Sample size is 2,269: Trial 954 (randomized 452, non-randomized 89, unspecified 413), Observational 498, Nonclinical toxicology 200, In-vitro/In-vivo/Ex-vivo 197, Chemistry: 193, Analysis 137, Trial follow-up 49, Pooled analysis 18, and Other 23.
3. This sample includes 88 AA studies, 14 Animal studies, 1,405 FDAAA safety studies, 449 PREA studies, and 313 PMCs.

Figure 1-13 shows some variations depending on the types of postmarketing studies—confirmatory studies for accelerated approvals (AA), PREA, FDAAA, and PMCs. Animal studies were excluded from the analysis because 100% of animal studies were observational. The vast majority of AA studies (84%) and PREA studies (89%) were clinical trials. When including trial follow-ups and analysis of clinical trials, the percentage of clinical trials went up to 95% for AA studies and 91% for PREA studies. These high percentages are found because most of AA studies are confirmatory trials and PREA studies are to establish indications/dosages for pediatric patients.





**Figure 1-13. Study design by PMR/PMC type (legal statute)**

Notes:

1. Animal studies were excluded from the analysis because all of animal studies are field studies (observational).
2. Sample size is 2,255 (14 animal studies are excluded from a total of 2,269 studies): FDAAA 1,405, PREA 449, PMC 313, and AA 88.

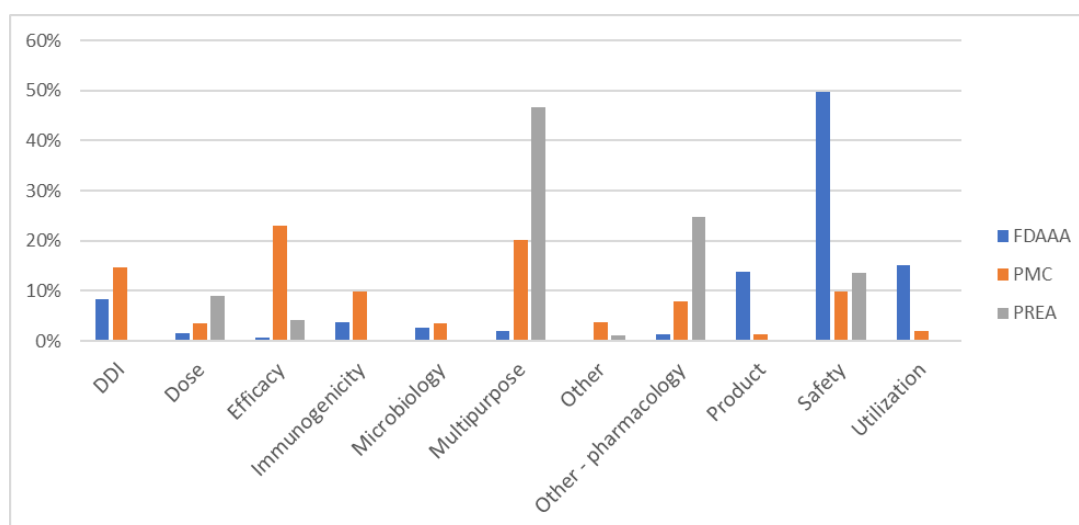
On the other hand, FDAAA studies have lower rate of clinical trials: 24% of FDAAA studies were clinical trials, 33% observational, 22% nonclinical toxicology and in-vitro/in-vivo/ex-vivo studies, and 13% chemistry, respectively. Since FDAAA studies are safety-related, it makes sense that many studies are observational or nonclinical toxicology studies. Chemistry studies are impurity/individual component analysis studies that were required under FDAAA. We observe that FDAAA requirements and PMCs have more various study designs than AA, Animal, or PREA studies because function and purpose of AA, Animal, and PREA studies are rather uniform.

### **Purpose of Studies**

The purpose of studies was classified based on study descriptions. The purpose of a total of 2,421 studies was determined. Among 2,421 studies, the most common rationale for

postmarketing studies was safety (34%) followed by multipurpose (15.3%), drug utilization (9%), product-chemistry (8%), drug-drug interaction (DDI) [7%], Pharmacology (5%), Confirmatory (4%), Dose (4%), Efficacy (4%), Immunogenicity (4%), and others (4%) including microbiology, biopharmaceutic, and pharmacology-safety studies. When including DDI, product-chemistry, pharmacology-safety, and utilization studies in safety studies, safety studies make up 52% of total postmarketing studies.

Figure 1-14 shows distributions of postmarketing study purpose by study types with the sample size of 2,311. Confirmatory studies for accelerated approvals (88) and animal studies (14) were excluded because the purpose of those studies is unitary—confirming clinical benefits. Biopharmaceutic studies were excluded due to a small sample size (8). Since the FDAAA studies are safety studies, 87% of the FDAAA requirements were clinical safety, DDI, drug utilization, and product-chemistry related studies. The remaining 13% were dose, immunogenicity, microbiology, multipurpose, other – pharmacology, and biopharmaceutic studies.



**Figure 1-14. Study purpose by PMR/PMC type**

Notes:

1. Confirmatory studies (88 accelerated approvals and 14 animal studies) were excluded from this graph because most of AA studies and animal studies are confirmatory studies.

2. Biopharmaceutic studies were excluded from this graph due to a small number of sample (8)
3. Sample size of 2,311: Drug-Drug Interaction (DDI) 165 (7%), Dose 86 (4%), Efficacy 105 (5%), Immunogenicity 85 (4%), Microbiology 49 (2%), Product 200 (9%), Safety 814 (35%), Utilization 220 (10%), Multipurpose 370 (16%), Pharmacology-Other and Pharmacology-Safety 193 (8%), and Other 24 (1%).
4. By study types, the sample of 2,311 was comprised of 1,405 FDAAA, 594 PREA, and 312 PMC studies.

PREA studies are more likely to investigate efficacy and dose (efficacy 4%, multipurpose 47%, pharmacology 25%, and dose 9%). Again, PREA studies are to support indications for pediatric patients and these studies often try to establish efficacy, safety, and pharmacokinetic / pharmacodynamic (PK/PD) activities at the same time. On the other hand, postmarketing commitments show more evenly distributed rationales. Twenty three percent of PMC were established to study efficacy, multipurpose 20%, DDI 15%, safety 10%, immunogenicity 10%, and pharmacokinetic/pharmacodynamic studies 8% respectively.<sup>61</sup>

#### 1.4.6 Length and size of studies

Some industry representatives note with concern that PMR/PMCs are getting longer and larger. In a *PharmaVoice*<sup>62</sup> interview, Peggy Schrammel<sup>63</sup> said “Postmarketing studies are often mandated as part of a regulatory commitment, and they can be larger, more complex, requiring more patients and longer follow-up times. It used to be a five-year study follow up was considered lengthy. Now it’s nothing to have 10 years to 15 years of follow up required....Sponsors are

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<sup>61</sup> The matrix of study design and purpose is provided in Figure 1-23 in Appendix B.

<sup>62</sup> PharmaVOICE.com is a Website for life-sciences executives and other healthcare-service related professionals. “The primary audience is made up of executive and corporate management from pharmaceutical, biotechnology, drug delivery, marketing communications, clinical services, contract research, drug development, and information technology companies, as well as other industry sectors.” [www.pharmavoice.com](http://www.pharmavoice.com)

<sup>63</sup> Peggy Schrammel, Vice President and Global Head, Portfolio Management, Peri-Approval Clinical Excellence (PACE) at PAREXEL. April 2011, on Uncovering the Value of Late-Phase Trials, Pharmavoice

challenged to come up with ways to get these studies done as quickly and as inexpensively as possible.”

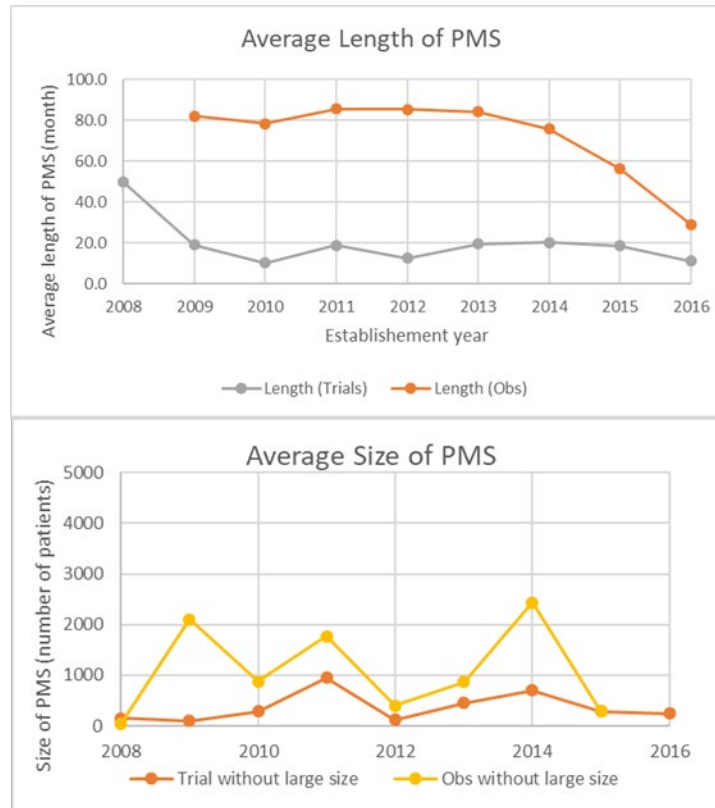
A total of 509 PMR/PMCs had information on the length of study and 275 PMR/PMCs had information on the sample size of study.<sup>64</sup> The average length was 34 months and the average sample size was 1,087. Observational studies lasted 74 months on average: clinical trials, 24 months and nonclinical trials, 17 month. Observational studies are usually long-term safety follow-up studies and it requires longer tracking of data.

I found three clinical trials with large sample size: 11,700 participants in a study assessing the serious risks for asthma, 10,300 patients in a study assessing cancer adverse events, and 9,000 patients in a type-2 diabetes study. Some long-term observational studies had bigger size requirements: 10,000 - 50,000 patients to assess serious adverse events.

Figure 1-15 shows the trend of the length and size of PMR/PMCs since 2008. There is no noticeable increasing trend in the length of studies. Rather, it is downward for observational studies and slightly downward for clinical trials. Excluding exceptionally large sizes (>10,000), there is no apparent trend in the size of studies.

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<sup>64</sup> For other studies, length and size data are not available in study description or study ID is not available to match with clinicaltrials.gov database. Thus, although there is no theoretical basis on linking data availability and the length/size of studies, there is a potential selection bias that this sample may not be representative of all postmarketing studies.



**Figure 1-15. Average length and size of PMR/PMCs**

Notes:

1. sample size for length = 509 and sample size for size of study = 275
2. I excluded the length data of observational studies in 2008 because there were only two observational studies with length information: one was 6-month-long antibody registry and the other one was 1-year observational study in pediatric patients.
3. I excluded 9 studies that are exceptionally large (sample size > 10,000): 1 in 2009, 3 in 2010, 4 in 2011, and 1 in 2012

As shown in Table 1-9 below, expedited approvals had longer postmarketing studies than traditional approvals, and requirements are longer than commitments. For expedited approvals, the average length was 38 months while for traditional approvals it was 30 months. Expedited approvals had longer clinical trials (29 months) than traditional approvals (15 months), while traditional approvals had longer observational studies (82 months) than expedited approvals (68 months). And, regardless of study designs, PMRs are longer than PMCs: the average length of PMRs was 34 months while the average length of PMCs was 24 months.

**Table 1-9. Average length and size of PMR/PMCs, by expedited vs. traditional, by requirement vs. commitment, and by trials vs. observational**

Categories		Average Length (months)	Average Size (number of patients)
Expedited	All	38	531
	Clinical trials	29	514
	Observational	68	1,011
	Requirements	39	602
	Commitments	34	385
Traditional	All	30	2,024
	Clinical trials	15	2,373
	Observational	82	7,914
	Requirements	32	2,191
	Commitments	6	271
Requirements	All	34	1,306
	Clinical trials	24	1,360
	Observational	76	4,322
Commitments	All	24	450
	Clinical trials	13	273
	Observational	45	1,900

Notes:

1. Average length for all postmarketing studies includes other types of studies than clinical trials and observational studies—i.e. nonclinical toxicology, analysis of data, etc.
2. The large number in the size of observational studies for traditional approval drugs includes three very large observational studies: sample sizes of 10,000, 40,000, and 50,000.

Regarding the size of studies, PMRs are larger than PMCs (1,306 for PMRs and 450 for PMCs), regardless of study designs. It is somewhat surprising that expedited approvals were smaller than for non-expedited, regardless of study design. But, in clinical trials, there were six large long-acting beta-agonists (LABA) trials for non-expedited respiratory drugs and five of them had 11,700 patients each and one of them had 6,200 patients involved. Without these LABA trials, the average size of traditional drugs was 347 which is smaller than expedited drugs. Moreover, in traditional approvals, three very large observational studies were found: sizes of 10,000, 40,000, and 50,000. Without these three outliers, the average size of observational studies for traditional drugs was 1,391 which is similar to the average size of observational studies for expedited drugs.

### 1.4.7 Compliance

#### **Status of Postmarketing Studies**

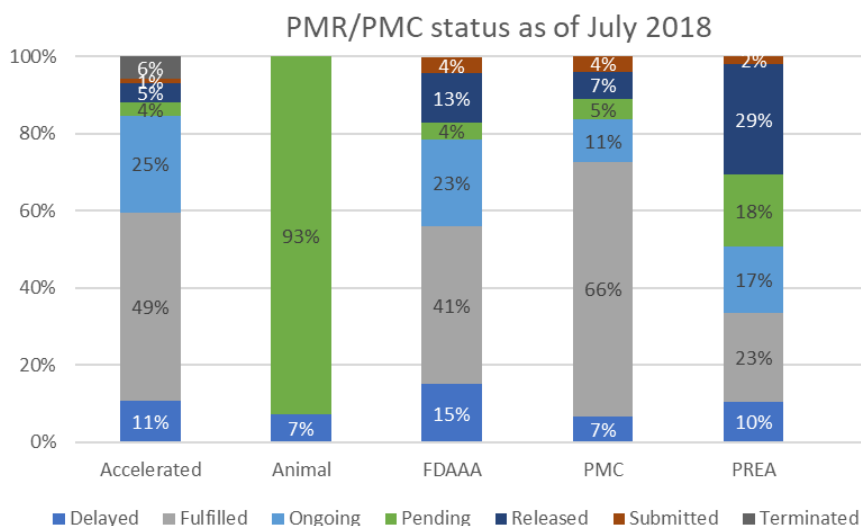
In the study sample of 2,814 PMR/PMCs, 54% of them were completed (39% fulfilled and 16% released), while 44% of the sample were open (19% ongoing, 12% delayed, 9% pending, and 3% submitted) as of July 2018. Among 2,814 studies, the current status for 54 studies (2%) were unknown. “Delayed” means the study missed a milestone and “pending” means the study has not begun but not delayed.

Figure 1-16 exhibits the current status of the postmarketing studies by types of studies, as of July 2018. About half of accelerated studies were fulfilled and a quarter are ongoing. Since most animal studies are field studies<sup>65</sup> in the case of occurrence of events, those studies are pending. Almost one third of PREA studies (29%) was released. The rationales for releasing PREA studies are largely unknown<sup>66</sup>. Also, a lower percentage of FDAAA safety requirements were fulfilled compared to PMCs.

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<sup>65</sup> One exception was immunogenicity study—the trial was completed on 10/1/2016, but the status is delayed perhaps due to the delay in submitting the final report.

<sup>66</sup> Sometimes, sponsors withdraw their NDA/BLAs or do not initiate studies for a long time. For example, FDA required the sponsor of OLEPTRO (NDA 22411) to study pediatric patients in 2010, but Sponsor requested withdrawal of the NDA. FDA acknowledged withdrawal request in letter dated 4/17/15. ---Per FDA letter dated 09/15/2017, this PMR has been released. Another example is Rezira (NDA 22442): Original Final Report Due Date was 09/30/2016; Deferral Extension granted per FDA letter dated 07/20/2016. But FDA sent letter of study release dated 10/30/2017 (reason unknown—the letter is not publicly available).



**Figure 1-16. PMR/PMC status by study types (as of July 2018)**

The difference in the percentage of fulfilled/released studies was observed in analysis studies whose samples are from other sources (e.g. spontaneous reports) and chemistry-product ingredient studies. Although not shown in the text, Figure 1-18 in Appendix B shows that the fulfillment rates are different among study designs: 32% of observational studies were fulfilled, while 59% of clinical trials were fulfilled and 80% of in-vitro/in-vivo/ex-vivo or nonclinical toxicology studies. In-vitro and animal studies are relatively straightforward to carry out compared to clinical studies and trials, thus a lower percentage of them were delayed. Observational studies often involve registries that take longer and pregnancy registries especially might take longer. (Figure 1-19 in Appendix B)

Figure 1-20 in Appendix B shows the PMR/PMC status by establishment year. Since some clinical trials and studies often takes years, it makes sense that more recent studies have lower ratio of fulfillment. I will examine fulfillment of studies below.

### **Fulfillment**



The status of ‘fulfilled’ means that FDA has reviewed the PMR/PMC final report and notified the sponsor that the PMR/PMC has been satisfied (see Table 1-2 in Section 1.2.1.1). In order to examine how many of PMR/PMCs were fulfilled and why some studies were delayed in further details, I looked at a sample of 680 PMR/PMCs that were established between July 2008 and December 2010 and followed up the status as of July 2018: this sample allows sufficient time (8-10 years) for closing out studies. Out of 680 studies, the status for 22 studies was undetermined. As of July 2018, 59% of the 658 studies established between July 2008 and December 2010 were fulfilled. If we include released studies (22% of the total), 81% of studies were closed after 8-10 years of establishment of studies. Eight per cent were ongoing, and 7% were delayed (see Figure 1-21 in Appendix B).

Table 1-10 shows how many studies were fulfilled or pending/delayed by study design (observational vs. clinical trial), by requirement vs. commitment, and by expedited vs. traditional. For all study designs, higher percentage of commitments were fulfilled (77%) compared to requirements (55%) which is somewhat surprising. For both clinical trials and observational studies, PMCs had slightly higher fulfillment and completion rate than PMRs. But, PMRs have lengthier requirements than PMCs (42 months for PMRs and 6 months for PMCs on average in the study cohort of 680 studies) and larger size of studies (2,241 patients for PMRs and 172 patients for PMCs on average in the study cohort of 680 studies) as expected from the findings in Section 1.4.6. Thus, PMRs might be more likely to be delayed than PMCs. when comparing expedited approvals with traditional approvals, 71% of postmarketing studies for expedited approvals were

fulfilled, while 53% for traditional approvals. Postmarketing studies for the expedited approvals are also less likely to be pending or delayed.<sup>67</sup>

**Table 1-10. Fulfilled and Pending/Delayed studies, by study design, requirement vs. commitment, and expedited vs. traditional (sample of the PMR/PMCs established Jul 2008 – Dec 2010)**

	Observational			Clinical Trial		
	Fulfilled	Pending/Delayed	Obs.Total	Fulfilled	Pending/Delayed	Trial total
PMR	25 (37%)	3 (4%)	68	82 (47%)	19 (11%)	176
PMC	1 (50%)	-	2	42 (68%)	7 (11%)	62
Expedited	6 (25%)	-	24	49 (72%)	5 (7%)	68
Traditional	19 (43%)	3 (7%)	44	66 (43%)	17 (11%)	152

Notes:

1. For all study designs, the ratio of fulfilled studies for requirements was 55%; 77% for commitments. The ratio of fulfilled studies for the expedited was 71%; 53% for traditional.
2. For all study designs, the ratio of released studies for requirements was 24%; 13% for commitments. The ratio of released studies for the expedited was 15%; 27% for traditional.

Table 1-11 presents categories/reasons of delays of 43 postmarketing studies. Fifty-one per cent were PREA studies, 33% FDAAA safety studies, and 16% PMCs. The rationales for delays were undetermined for 10 PREA studies. Among 33 delayed studies, the most frequently cited reason was continuing discussion on study design and protocol (45%) followed by marketing status change (24%) and patient recruiting (21%). Delay due to study design and protocol occurred in FDAAA safety studies more often.

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<sup>67</sup> In observational studies, there was no delayed or pending studies for the expedited approvals: 10 ongoing, 1 submitted, and 7 released. For traditional approvals, there was 3 observational studies delayed (FDAAA safety studies). No obvious qualitative difference was observed between observational studies for expedited approvals and ones for traditional approvals.

**Table 1-11. Reasons of delays (sample size: 43)**

Category	Reasons	Additional information
Marketing	Sponsor change (4)	4 PREA studies
	Withdrawal/Discontinuation (4)	2 PREA and 2 PMC studies
Enrollment	Recruiting patients (7)	2 FDAAA (pregnancy registry, pediatric safety), 2 PREA, and 3 PMC studies (all randomized trials studying efficacy)
Protocol	Study design and protocol (15)	Often continuing discussions on study design and protocol between FDA and sponsors. 11 FDAAA (7 trials, 1 nonclinical toxicology, 2 registries, 1 safety data analysis), 2 PREA, and 2 PMC studies (2 pediatric studies)
Replaced	Replaced with new study (2)	These 2 PREA studies were replaced with new ones. Not yet released.
Unsatisfactory	Final report submitted, but not fulfilled (1)	For this PREA study, the final report was submitted on 5/27/2016, but did not fulfill the requirement.
Undetermined	Good cause, deferral extension granted by FDA (7)	6 PREA studies (reasons unknown, FDA granted the deferral extension requests), 1 FDAAA study (the final report due date was missed because of the need to correct the safety datasets to adhere the data standards)
	Deferral extension denied by FDA (3)	All PREA studies. Sponsors requested deferral extension, but FDA denied.

More postmarketing studies might be fulfilled when sufficient time is allowed. Let us look at PMRs to compare the findings of this study with the OIG study (2016) and the Wallach et al. (2018) study, both of which looked only at PMRs. In this study, I found that 55% of PMRs established July 2008 – December 2010 were fulfilled as of July 2018, allowing 7.5 to 10 years. OIG (2016) found that 23% of PMRs established FY 2008 – 2014 were fulfilled as of September 2014 which allowed maximum 0-6 years. But, OIG study didn't allow sufficient time for some studies to be fulfilled—e.g., some studies established in 2014 are not likely to be fulfilled as of September 2014. And, Wallach et al. (2018) discovered that 38% of PMRs established 2009 – 2012 were fulfilled as of November 15, 2017 which allows maximum 5-8 years. They studied PMRs for new drugs only, thus comparison with OIG study or the findings from this study may not be accurate.

## 1.5 Discussion and Conclusion

In this paper, I reviewed all postmarketing requirements and commitments that were established between July 2008 and May 2016 for NDAs, BLAs, and supplements. While it is said that postmarketing studies have been increasing, this study provides a more complete review of recent studies than has been available.

The percentage of NMEs approved with postmarketing studies has been increasing since the 1970s, but not particularly since the FDAAA of 2007. The total number PMR/PMCs has been increasing since 2008, a trend that can be attributed to studies established for existing drugs rather than new drugs and to required studies rather than to commitments. There was no apparent increase in the average number of postmarketing studies per drug approval. To some extent, the increase in the number of postmarketing studies can be attributed to class actions—i.e. safety studies on opioid drugs and impurity studies on parenteral nutrition/critical care drugs.

At least since 2008, there is no evidence for the claim that postmarketing studies are getting larger and longer. It could be a longer-term trend when looking at data for the past couple of decades, however. Compared to PMCs, PMRs are longer and larger. Also, expedited approvals had longer studies compared to traditional approvals, but the average size was smaller due to a couple of huge size studies imposed on traditional approvals.

Furthermore, expedited approvals are more likely to have postmarketing studies than traditional approvals. And, expedited approvals had more requirements than commitments compared to traditional approvals, excluding PREA studies. Moreover, PMR/PMCs for expedited approvals are more likely to be fulfilled, released, or submitted and less likely to be delayed. These facts at least do not aggravate the concerns that drugs are getting approved fast (perhaps with less requirements) and studies are not done for these drugs.

In addition, 59% of postmarketing studies were fulfilled, when allowed 8-10 years. And this is somewhat encouraging because other studies showed lower percentage of fulfilled postmarketing requirements (they allowed shorter time). This may sooth some concerns about enforcement raised in studies conducted by OIG, GAO, BAH, Moore and Furberg (2014), and Darrow et al. (2014).

The findings on compliance appear to contradict what two industry representatives said during interviews. They said that incentives for fulfilling postmarketing studies quickly wane and people do not care about PMR/PMCs after approval. BAH's interview (2008) with some FDA reviewers also revealed that "some reviewers speculated that the lack of an enforcement mechanism to deal with sponsor noncompliance influenced some sponsors to be less timely in completing their commitments." Sertkaya et al. (2014) also noted that "FDA is justifiably worried about the problematic history of pharmaceutical company promises about post-marketing clinical trials, as some companies have drawn out the process of designing post-market clinical trials for many years." This discrepancy might be due to the fact that FDA's efforts to enforce compliance are relatively recent. The OIG (2016) study also noted that sponsors are making progress toward completing most PMRs.

In the meantime, the FDA appears reluctant to issue warning or noncompliance letters to sponsors. According to OIG report (2016), FDA sent 32 noncompliance letters to sponsors of PMRs in 2014.<sup>68</sup> Twenty-two of them were notification of noncompliance with PREA PMRs and 8 were for FDAAA safety PMRs. Not all delayed postmarketing study requirements resulted in

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<sup>68</sup> It is hard to know the denominator. But, among 1,256 PMRs established 2008-2014, as of 2014, 7% (90) were delayed. Since this is the percentage of PMRs delayed at a given time (not accumulated), the percentage of once-delayed PMRs at any given time would be higher. Among 90, 32 were delayed for 1 year, 34 for 2 years, and 24 for 3-5 years. 32 letters were issued for 9 PMRs (9 PMRs out of 90 delayed PMRs).

noncompliance action.<sup>69</sup> FDA also issued only one warning letter related to PMRs established from 2008 to 2014, according to OIG.<sup>70</sup>

In sum, what has been said about postmarketing studies needs to be updated. Although the total number of PMR/PMCs have increased since FDAAA, the percentage of new drugs with PMR/PMCs or the average number of PMR/PMCs per drug has not increased. Since 2008, the number of postmarketing studies has increased because the FDA established PMR/PMCs for already-marketed drugs (not new drug approvals) and class actions such as opioid studies and impurity studies played a large role. Also, PMR/PMCs are not getting longer nor larger since the FDAAA of 2007. And, 59% of postmarketing studies were fulfilled, which is higher than previously known.

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<sup>69</sup> “A sponsor of a delayed PMR may nonetheless be in compliance if, for example, the PMR is an FDAAA PMR, and the sponsor has demonstrated good cause for delay.” (OIG, 2016)

<sup>70</sup> “Prior to issuing that warning letter, FDA sent seven written correspondences to the sponsor from May 2010 to February 2012 in an attempt to resolve questions about a PMR.... In the warning letter, FDA informed the sponsor that the product was misbranded due to the sponsor’s violation of section 505(o) of the FD&C Act. The final correspondence from FDA is a close-out letter sent 1 year after the warning letter and 11 months after the sponsor’s response to the warning letter.” (OIG, 2016)

## Bibliography for Study 1

- Booz Allen Hamilton. (2008). Independent Evaluation of FDA's Prescription Drug User Fee Act – Evaluations and Initiatives; CDER Technical Support and Analysis -- Final Report on the PMR/PMC Backlog Review. Retrieved from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM181135.pdf>
- Carpenter, D., Zucker, E. J., & Avorn, J. (2008). Drug-review deadlines and safety problems. *New England Journal of Medicine*, 358(13), 1354-1361.
- Carpenter, D., Chattopadhyay, J., Moffitt, S., & Nall, C. (2012). The complications of controlling agency time discretion: FDA review deadlines and postmarket drug safety. *American Journal of Political Science*, 56(1), 98-114.
- Carpenter, D. (2014). Reputation and power: organizational image and pharmaceutical regulation at the FDA (Vol. 137). Princeton University Press.
- Carpenter, D. (2014). Can expedited FDA drug approval without expedited follow-up be trusted?. *JAMA internal medicine*, 174(1), 95-97.
- Carpenter, D. P., & Krause, G. A. (2012). Reputation and public administration. *Public administration review*, 72(1), 26-32.
- Collier, R. (2009). Rapidly rising clinical trial costs worry researchers. *Canadian Medical Association Journal*, 180(3), 277-278.
- CSDD, Kaitin KI, editor. FDA requested postmarketing studies in 73% of recent new drug approvals. Tufts Center for the Study of Drug Development Impact Report. 2004 July/August;6(4)
- CSDD, Kaitin KI, editor. Challenges loom for postmarketing study commitments; benefits unclear. Tufts Center for the Study of Drug Development Impact Report. 2007 May/June;9(3)
- CSDD, Kaitin KI, editor. Postmarketing studies are becoming the norm in U.S., Europe, and Japan. Tufts Center for the Study of Drug Development Impact Report. 2008 July/August;10(4)
- Darrow, J. J., Avorn, J., & Kesselheim, A. S. (2014). New FDA breakthrough-drug category—implications for patients. *New England Journal of Medicine*, 370(13), 1252-1258.
- Fain, K., Daubresse, M., & Alexander, G. C. (2013). The food and drug administration amendments act and postmarketing commitments. *Jama*, 310(2), 202-204.

- Fan, Y., Sun, B., Agarwal, S., & Zhang, L. (2016). Review of Transporter-Related Postmarketing Requirement or Postmarketing Commitment Studies. *The Journal of Clinical Pharmacology*, 56(S7).
- US Food and Drug Administration (2004). Innovation or stagnation. Challenge and Opportunity on the Critical Path to New Medical Products. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf>
- US Food and Drug Administration (2011). Guidance for industry: postmarketing studies and clinical trials—implementation of §505(o)(3) of the Federal Food, Drug, and Cosmetic Act (April 2011). Retrieved from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.
- U.S. Government Accountability Office (2009). NEW DRUG APPROVAL: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints. September 2009. GAO-09-866. Retrieved from <http://www.gao.gov/assets/300/295762.pdf>
- U.S. Government Accountability Office (2015). FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement. December 2015. GAO-16-192. Retrieved from <http://www.gao.gov/products/GAO-16-192>.
- Gottlieb, S. (2016) FDA Needs to Change How it Regulates Novel Technologies. *Forbes*. Jan 12, 2016 <https://www.forbes.com/sites/scottgottlieb/2016/01/12/fda-needs-to-change-how-it-regulates-novel-technologies/#2636756c191e>
- Institute of Medicine (2007). The Future of Drug Safety: Promoting and Protecting the Health of the Public. Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice, Institute of Medicine.
- Institute of Medicine (2012). Ethical and Scientific Issues in Studying the Safety of Approved Drugs. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, Board on Population Health and Public Health Practice, Institute of Medicine. Retrieved from [http://www.ncbi.nlm.nih.gov/books/NBK200905/pdf/Bookshelf\\_NBK200905.pdf](http://www.ncbi.nlm.nih.gov/books/NBK200905/pdf/Bookshelf_NBK200905.pdf)
- Johnson, J. R., Ning, Y. M., Farrell, A., Justice, R., Keegan, P., & Pazdur, R. (2011). Accelerated approval of oncology products: the food and drug administration experience. *Journal of the National Cancer Institute*, 103(8), 636-644.
- Kesselheim, A. S., Wang, B., Franklin, J. M., & Darrow, J. J. (2015). Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ* 2015;351:h4633.
- Kesselheim, A. S., & Darrow, J. J. (2015). FDA designations for therapeutics and their impact on drug development and regulatory review outcomes. *Clinical Pharmacology & Therapeutics*, 97(1), 29-36.



- Lipsky, M. S., & Sharp, L. K. (2001). From idea to market: the drug approval process. *The Journal of the American Board of Family Practice*, 14(5), 362-367.
- Lo, B. (2015). Sharing clinical trial data: maximizing benefits, minimizing risk. *Jama*, 313(8), 793-794.
- Mattison, N., & Richard, B. W. (1987). Postapproval Research Requested by the FDA at the Time of NCE Approval, 1970–1984. *Drug Information Journal*, 21(3), 309-329.
- Moore, T. J., & Furberg, C. D. (2014). Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US Food and Drug Administration: the class of 2008. *JAMA internal medicine*, 174(1), 90-95.
- Office of Inspector General (1996). Postmarketing Studies of Prescription Drugs. U.S. Department of Health and Human Services. May 1996. OEI-03-94-00760.
- Office of Inspector General (2006). FDA’s Monitoring of Postmarketing Study Commitments. U.S. Department of Health and Human Services. June 2006. OEI-01-04-00390.
- Office of Inspector General (2016). FDA is issuing more postmarketing requirements, but challenges with oversight persist. July 2016. OEI-01-14-00390. <https://oig.hhs.gov/oei/reports/oei-01-14-00390.pdf>
- Sertkaya, A., Birkenbach, A., Berlind, A., & Eyraud, J. (2014). Examination of clinical trial costs and barriers for drug development. Report, US Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Washington, DC.
- Wallach, J. D., Ross, J. S., & Naci, H. (2018). The US Food and Drug Administration’s expedited approval programs: Evidentiary standards, regulatory trade-offs, and potential improvements. *Clinical Trials*, 15(3), 219-229.

## Appendix A for Study 1: Tables

**Table A-12. Number of PMS by NDA and BLA by approval year, all new and supplemental approvals**

YEAR	PMS	PMS with NDAs	PMS with BLAs	NDAs with PMS	BLAs with PMS
2008	104	97 (93%)	7	42	2
2009	286	233 (81%)	53	76	12
2010	290	232 (80%)	58	72	14
2011	327	258 (79%)	69	79	23
2012	295	267 (91%)	28	73	9
2013	335	306 (91%)	29	76	11
2014	372	319 (86%)	53	103	16
2015	499	440 (88%)	59	292	25
2016	306	280 (92%)	24	51	8
<b>Total</b>	<b>2,814</b>	<b>2,434 (86%)</b>	<b>380</b>	<b>864</b>	<b>120</b>

Note: This table shows the number of NDA and BLAs (new and supplemental) associated with PMR/PMCs established between July 2008 and May 2016.

**Table A-13. Number of PMS by new and supplemental approvals**

YEAR	PMS	PMS with new	PMS with suppl.	New approval with PMS	Suppl. approval with PMS
2008	104	67	37	23	21
2009	286	241	45	61	27
2010	290	232	58	59	27
2011	327	264	63	75	27
2012	295	243	52	60	22
2013	335	283	52	62	25
2014	372	313	59	86	33
2015	499	419	80	267	50
2016	306	293	13	49	10
<b>Total</b>	<b>2,814</b>	<b>2,355</b>	<b>459</b>	<b>742</b>	<b>242</b>

Note: This table shows the number of new and supplemental approvals (for both NDAs and BLAs) associated with PMR/PMCs established between July 2008 and May 2016.

**Table A-14. Number of postmarketing studies for expedited approvals by study type**

	Accelerated	Animal	FDAAA	PREA	PMR total	PMC	TOTAL
Orphan	69	5	406	11	<b>491</b>	<b>163</b>	654
Accelerated	85	-	110	2	<b>197</b>	<b>40</b>	237
Breakthrough	19	-	60	9	<b>88</b>	<b>41</b>	129
Fast track	30	3	274	57	<b>364</b>	<b>111</b>	475
Priority	67	6	530	138	<b>741</b>	<b>228</b>	969
Total (expedited)	85	7	628	148	<b>868</b>	<b>241</b>	1109
Total (non-expedited)	-	-	594	548	<b>1,142</b>	<b>121</b>	1,263

Notes: Orphan, Accelerated, Breakthrough, Fast track, and Priority approval pathways can be applied to a drug application at the same time. Therefore, the sum of all postmarketing studies for expedited approvals is not same as total PMR/PMCs associated with expedited approvals.

**Table A-15. Disease Classification**

ICD-10 disease class	After simplification
Blood & Immune	Blood & Immune
Cancer	Cancer
Circulatory	Circulatory
Digestive	Digestive
Endocrine, Nutrition, Metabolic	Endocrine, Nutrition, Metabolic
Eye & Adnexa	Other
Genitourinary	Reproductive, Urology, & Pregnancy
Imaging, Radio, Contrast	Imaging, Radio, Contrast
Infectious & Parasite	Infectious & Parasite
Injury, Poisoning, Other external	Other
Mental, Behavioral, Neurodevelopmental	Psychiatry & Neurology
Musculoskeletal & Connective Tissue	Musculoskeletal, connective tissues, & dermatology
Nervous	Psychiatry & Neurology
Pain & Anesthesia	Pain & Anesthesia
Parenteral Nutrition, Critical Care	Parenteral Nutrition, Critical Care
Pregnancy & Childbirth	Reproductive, Urology, & Pregnancy
Respiratory	Respiratory
Skin & Subcutaneous tissue	Musculoskeletal, connective tissues, & dermatology
OTHER	Other

Note: After combining relevant disease classes, 14 disease classifications were identified.

**Table A-16. Number of postmarketing studies, by PMS types and by disease class**

<b>Disease Class</b>	<b>AA</b>	<b>Animal</b>	<b>FDAAA</b>	<b>PREA</b>	<b>PMR total</b>	<b>PMC</b>	<b>Total</b>
Blood & Immune	10	-	38 (55%)	10	58	11	69
Cancer	65	-	239 (58%)	-	304	109	<b>413</b>
Circulatory	2	-	42 (51%)	32	76	6	82
Digestive	3	-	52 ( <b>32%</b> )	79	134	29	163
Endocrine, Metabolism	5	-	160 (58%)	72	237	38	275
Imaging	-	2	21 (58%)	7	30	6	36
Infectious	1	12	151 (42%)	126	290	73	<b>363</b>
Musculoskeletal & Dermatology	-	-	86 (51%)	58	144	25	169
Other	-	-	16 (29%)	21	37	18	55
Pain & Anesthesia	-	-	350 ( <b>74%</b> )	118	468	4	<b>472</b>
Parenteral Nutrition, Critical care	-	-	196 ( <b>98%</b> )	5	201	-	201
Psychiatry & Neurology	-	-	168 (42%)	176	344	56	<b>400</b>
Reproductive, Urology, & pregnancy	2	-	20 (41%)	17	39	10	49
Respiratory	-	-	12 ( <b>18%</b> )	52	64	3	67
<b>Grand Total</b>	<b>88</b>	<b>14</b>	<b>1551</b>	<b>773</b>	<b>2,426</b>	<b>388</b>	<b>2,814</b>

**Table A-17. Number of postmarketing studies, by year and disease class**

<b>DISEASE CLASS</b>	<b>Total PMS</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>2011</b>	<b>2012</b>	<b>2013</b>	<b>2014</b>	<b>2015</b>	<b>2016</b>	<b># of NDA/BLAs</b>	<b>Average</b>
Blood & Immune	69	12	7		14	8	2	5	15	6	21	3.3
Cancer	413	12	35	32	72	63	66	58	54	21	85	4.9
Circulatory	82	2	22	4	16	8	4	17	8	1	28	2.9
Digestive	163	1	18	28	20	37	18	18	8	15	41	4.0
Endocrine, Metabolism	275	10	37	36	13	43	36	55	43	2	77	3.6
Imaging	36	5		2	5	2	2	1	19		28	1.3
Infectious	363	18	31	34	45	42	50	83	45	15	103	3.5
Musculoskeletal & Dermatology	169	2	37	29	20	12	22	18	19	10	48	3.5
Pain & Anesthesia	472	9	31	26	28	18	82	51	22	205	78	6.1
Parenteral Nutrition, Critical care	201				4		9	9	179		182	1.1
Psychiatry & Neurology	400	21	58	75	65	25	37	38	54	27	106	3.8
Reproductive, Urology, & pregnancy	49	2	3	7	9	14	3	4	6	1	23	2.1
Respiratory	67	1	6	7	6	16	1	10	17	3	23	2.9
Other	55	9	1	10	10	7	3	5	10		21	2.6
<b>Total</b>	<b>2814</b>	<b>104</b>	<b>286</b>	<b>290</b>	<b>327</b>	<b>295</b>	<b>335</b>	<b>372</b>	<b>499</b>	<b>306</b>	<b>864</b>	<b>3.3</b>

Notes: Reasons for hikes in certain drug classes in a particular year:

Nervous disease, 2010: Botox drug class

Pain & Anesthesia, 2014 and 2016: class actions – opioid related

Parenteral, Critical care, 2015: class actions – impurity related

Infectious disease, 2014: no class action, but more drugs were approved

**Table A-18. Variable description**

Variable	Description and coding rules	Comments
Newness of study	<ul style="list-style-type: none"> <li>a. New: new study established</li> <li>b. Ongoing/Existing: ongoing or existing studies</li> <li>c. Sub-study: a study within a study</li> <li>d. Follow-up: follow-up on registry or clinical trials</li> <li>e. Unknown/undetermined</li> </ul>	
Study Function	<ul style="list-style-type: none"> <li>a. Conduct: conduct a new study</li> <li>b. Develop/validate methods: develop and/or validate a method</li> <li>c. Submit: submit data and/or report (final report or analysis) from existing study</li> <li>d. Unknown/undetermined</li> </ul>	
Study Category	<ul style="list-style-type: none"> <li>a. Conducting new study</li> <li>b. Conducting ongoing/existing study</li> <li>c. Conducting sub-study</li> <li>d. Conducting follow-up</li> <li>e. Submitting report, ongoing/existing study</li> <li>f. Submitting report, sub-study</li> <li>g. Submitting report, follow-up</li> <li>h. Developing or validating method or measure</li> </ul>	A follow-up study is
Study Design	<ul style="list-style-type: none"> <li>a. RCT: randomized controlled clinical trial</li> <li>b. Non-R clinical trial: non-randomized clinical trial</li> <li>c. Trial, unspecified: clinical trial (randomization unspecified)</li> <li>d. Observational: A type of clinical study in which participants are identified and assessed for biomedical or health outcomes. Unlike trials, the investigator does not assign participants to a specific interventions/treatment.</li> <li>e. Nonclinical toxicology: animal toxicology study</li> <li>f. In Vivo/In Vitro/Ex Vivo</li> <li>g. Chemistry: studies that are related to product quality and control such as product impurity, product stability, batch test, etc.</li> <li>h. Trial follow-up: follow-up on existing/ongoing trial(s)</li> <li>i. Pooled analysis: pooled analysis, sampling from existing/ongoing studies and/or literature</li> <li>j. Other: all other study designs</li> <li>k. Undetermined: design unspecified, undetermined</li> </ul>	<p>“Other” study design includes developing method/algorithm, patient instruction, usability study, feasibility, collecting data, product batch test, expansion, literature, gathering expert group opinions, food effect studies, etc.</p>

Variable	Description and coding rules	Comments
Study purpose	<ul style="list-style-type: none"> <li>a. Safety: studies that address safety (risks) of drugs</li> <li>b. Efficacy: studies that address efficacy (the primary endpoints of most of randomized trials are efficacy related)</li> <li>c. Confirmatory: studies confirming clinical benefits -- accelerated approvals and animal approvals</li> <li>d. Multipurpose: multiple purposes</li> <li>e. DDI: drug-drug interaction</li> <li>f. Dose: dosage</li> <li>g. Immunogenicity: anti-drug antibody studies, antigen processing, developing and validating method to study immunogenicity</li> <li>h. Microbiology: susceptibility, drug resistance, phenotype/genotype analyses, substitution, virologic failure</li> <li>i. Biopharmaceutics: bioavailability, bioequivalence, and food effect studies</li> <li>j. Utilization: developing and validating measures/codes for misuse, abuse, addiction, and overdose, general drug utilization studies, epidemiologic studies on misuse and abuse, etc.</li> <li>k. Product: product quality and control studies such as product impurity, product stability, batch test, etc. as well as developing methods for determining individual component</li> <li>l. Other – pharmacology: PK/PD general, exposure-response, biomarkers, ADME (absorption, distinction, metabolism, and excretion), and mass balance studies</li> <li>m. Other: all other – e.g. administration method, withdrawal, dose equivalence, assay development, dependence, etc.</li> <li>n. Undetermined: study purpose is unclear</li> </ul>	<p>* Studies on the risk of misuse and overdose are classified as “safety” study</p> <p>* Studies on individual component of all batches are included in “other” category</p>
Pediatric safety	PREA studies and non-PREA studies that address pediatric safety – i.e. embryo-fetal studies, pre and post-natal studies, pregnancy registry, pediatric safety (ages 0-17)	
Pediatric efficacy	PREA studies and non-PREA studies that address efficacy for pediatric patients (ages 0-17)	
Length of study	The length of study stated in study description OR in clinicaltrials.gov database (start date – actual primary completion date) N/A, if unknown	
Size of study sample	The sample size mentioned in study description OR in clinicaltrials.gov database (sample size) N/A, if unknown	

Variable	Description and coding rules	Comments
Disease (drug class)	Based on ICD-10 (WHO standard), approved indications were classified – 14 classifications Blood & Immune Cancer Circulatory Digestive Endocrine, Metabolism Imaging Infectious Musculoskeletal & Dermatology Pain & Anesthesia Parenteral Nutrition, Critical care Psychiatry & Neurology Reproductive, Urology, & pregnancy Respiratory Other	
PMR/PMC type	FDAAA (safety study, required) AA (confirmatory study, required) Animal (field study to confirm, required) PREA (pediatric study, required) PMC – commitment	
PMR or PMC	FDAAA, AA, Animal, PREA = 1 (required) PMC = 0 (committed)	
Approval date	The date of drug-approval associated with a PMR/PMC	
Original approval date	Original approval date of a drug	
Establishment date	Establishment date provided by FDA if available For PMR/PMCs without date info, establishment date was coded by the following rules: a. Find class action dates on FDA website and match PMS with the date b. If approval date = the first appeared quarter of the year, I took the approval date as establishment date c. For others, check approval documents to get the date of PMR/PMCs officially established d. If approval letters not found, get all quarterly data -- merge all, allow duplications, then find the time the study first appears in the quarterly dataset name	
PMS status	The current status of a PMR/PMC: Pending Ongoing Delayed Submitted Released Terminated Fulfilled N/A, if unknown	
Fulfilled	1 if fulfilled, 0 if not fulfilled, N/A if unknown	
Released	1 if released, 0 if not released, N/A if unknown	
Terminated	1 if terminated, 0 if not terminated, N/A if unknown	
Delayed without good cause	Not delayed: the PMR/PMC is not delayed 1: delayed without good cause 0: delayed with good cause Undetermined: status is unknown or whether or not the delay had a good cause is undetermined N/A if no info is available	
Orphan	1 if orphan, 0 if not orphan,	

Variable	Description and coding rules	Comments
Accelerated	1 if accelerated approval, 0 if not accelerated	
Fast track	1 if fast track approval, 0 if not fast track, N/A if unknown	
Breakthrough	1 if breakthrough approval, 0 if not breakthrough	
Priority	1 if priority review was given, 0 if not priority review	
Expedited approval	1 if any of expedited programs applied 0 if none of expedited programs applied N/A if unknown	
NME	1 if NME 0 if not NME N/A if unknown	All supplemental approvals are non-NME.  There is no information for one drug DOLOPHINE HYDROCHLORIDE (approved in 1947) whether the drug was NME at the time of approval
Marketing status	Prescription OTC (over-the-counter) Discontinued N/A if unknown	

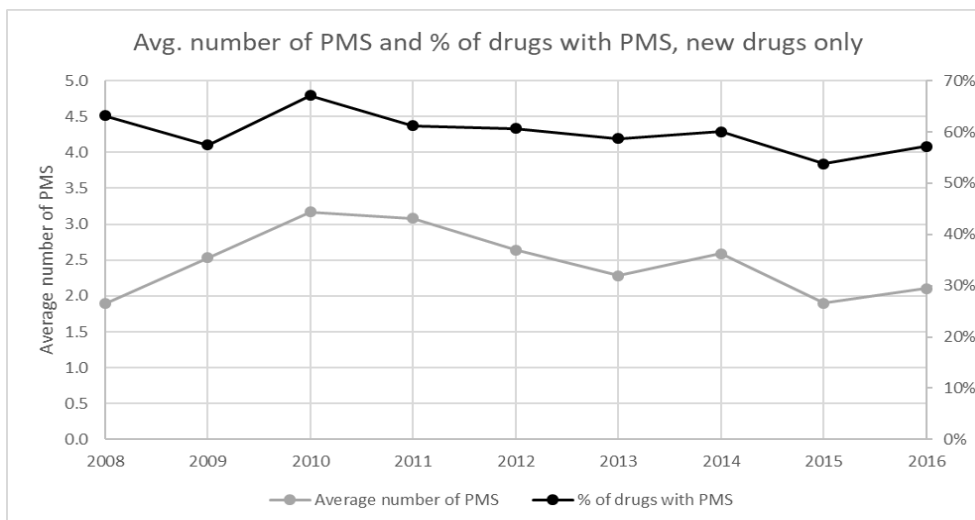
**Table A-19. Example of PMR/PMCs for Afinitor (NDA #22334)**

PMR/PMC	Study types	Study description
PMC	PMC	Conduct a 3 - arm randomized trial investigating the combination of everolimus with exemestane versus everolimus alone versus capecitabine in patients with estrogen - receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole.
PMR	FDAAA	Conduct a trial in patients with severe hepatic impairment (Child Pugh Class C). This trial need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.
PMC	PMC	Submit a final report, including datasets, for the final overall survival results from trial CRAD001Y2301 (BOLERO-2).
PMR	AA	Submit the final report (at least 4 years of follow-up) and datasets from M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with everolimus versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).
PMC	PMC	Submit the final, per-protocol overall survival analysis of protocol C2240 which was to be conducted 2 years after randomization of the last patient.
PMR	AA	Submit the long-term (at least 5 years) follow-up efficacy and safety data from C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).
PMR	FDAAA	Submit the results of the final analysis of overall survival data from RAD001C2324 to further characterize the safety and efficacy profile of everolimus in pancreatic neuroendocrine tumors.



PMR/PMC	Study types	Study description
PMR	FDAAA	Submit the results of the final analysis of overall survival data from RAD001C2325 to further characterize the safety and efficacy profile of everolimus in carcinoid tumors.
PMR	AA	To complete the ongoing clinical trial CRAD001M2302 entitled "A Randomized, Double-blind, Placebo-controlled Study of RAD001 in the Treatment of Angiomyolipoma in Patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM)" to further verify and describe the ultimate clinical outcomes of the duration of objective responses, incidence of nephrectomy and of renal embolization four years after randomization of the last patient in the study, as specified in the original protocol. You will submit the final comprehensive clinical study report, inclusive of all data collected in the clinical trial, as described in ICH E3.
PMR	FDAAA	To evaluate the potential for serious risk of adverse long-term effects of Afinitor (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with Afinitor (everolimus) in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).
PMR	FDAAA	To evaluate the potential for serious risk of adverse long-term effects of Afinitor (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with Afinitor (everolimus) versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).
PMC	PMC	To submit the clinical study report and datasets for the final analysis of overall survival (OS) for Trial CRAD001T2302, entitled "A randomized, double-blind, multicenter, phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin - RADIANT-4," and to include the final OS data in the product label.

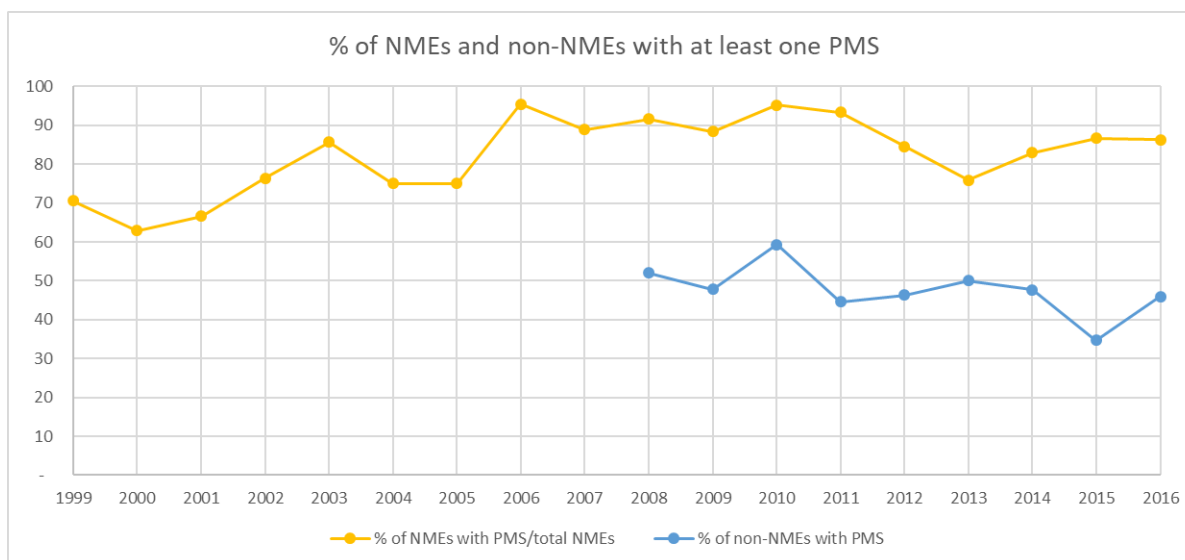
## Appendix B for Study 1: Figures



**Figure B-17. Average number of PMS and % of drugs with PMS, new drug approvals (original NDA/BLAs),**

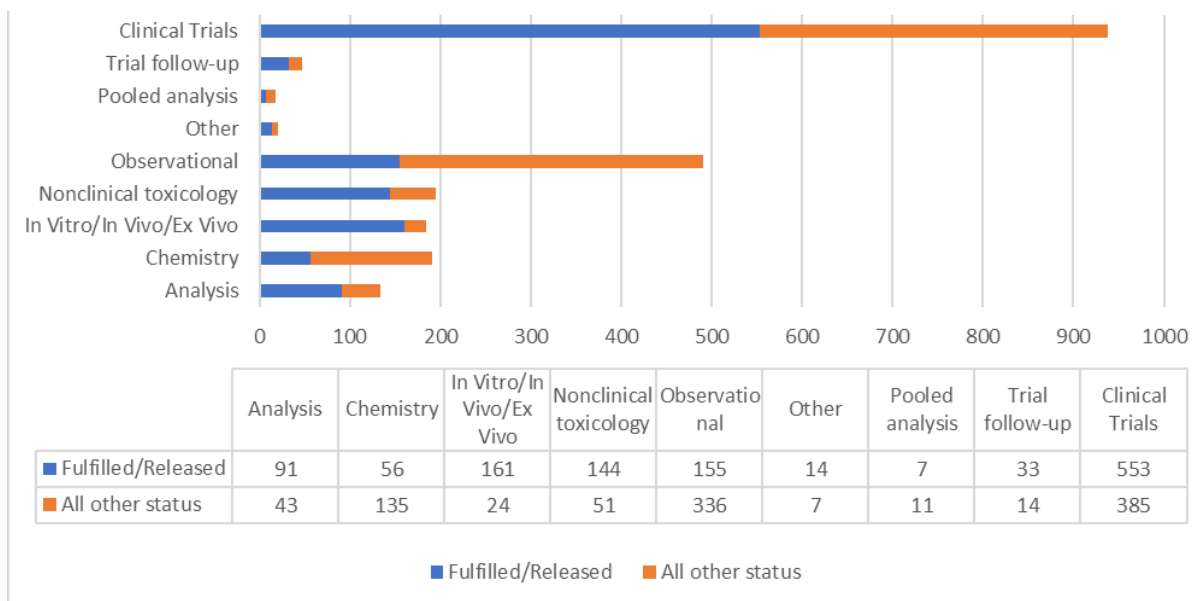
**July 2008-May 2016**

Notes: This figure shows the average number of PMS per original NDA/BLA approved by CDER and the percentage of new drug approvals that have at least one PMS between July 2008 and May 2016. There is no notable trend in the average number of PMS per new drug approval.



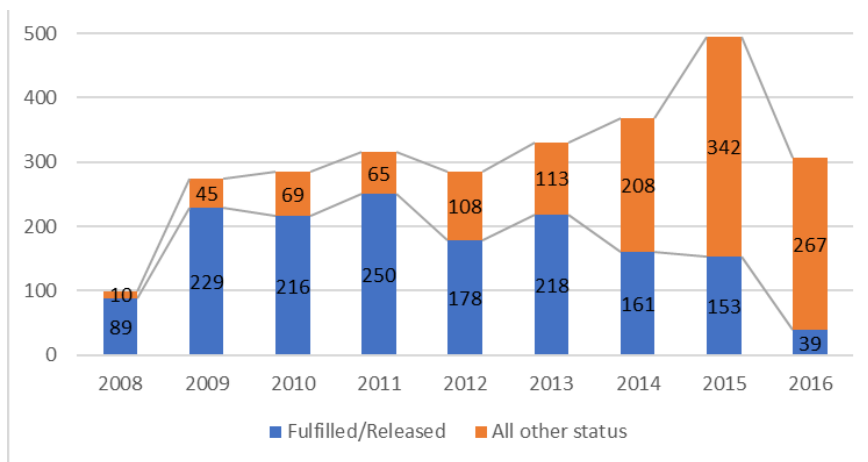
**Figure B-18. Number of PMR/PMCs established, by chemical type (NME vs. non-NME)**

Notes: This figure compares NMEs and non-NMEs with PMS. The percentage of NMEs with PMS has decreased after the FDAAA until 2013 and it has increased since 2013. The percentage of non-NMEs with PMS is slightly downward since 2008 despite some fluctuations.

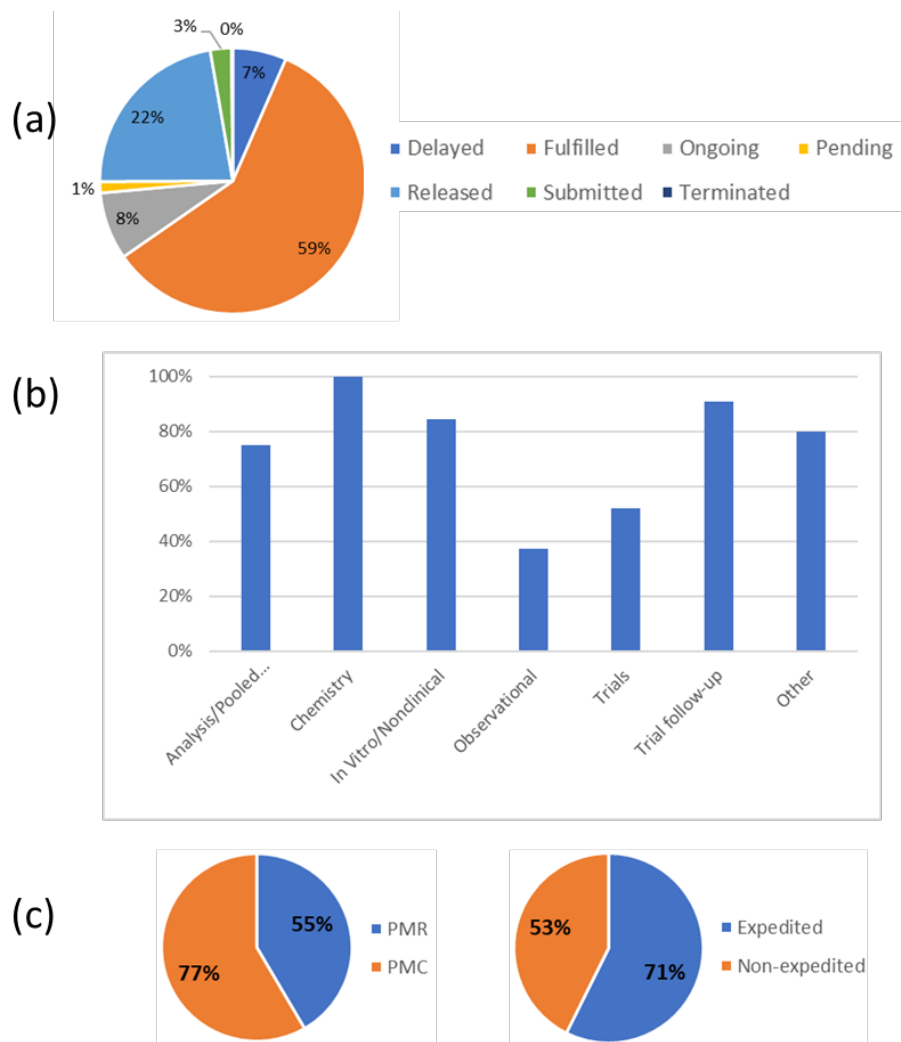


**Figure B-19. PMR/PMC status by study design, as of July 2018**

Note: the sample size is 2,267 excluding 547 PMR/PMCs without study design info out of a total of 2,814 studies.

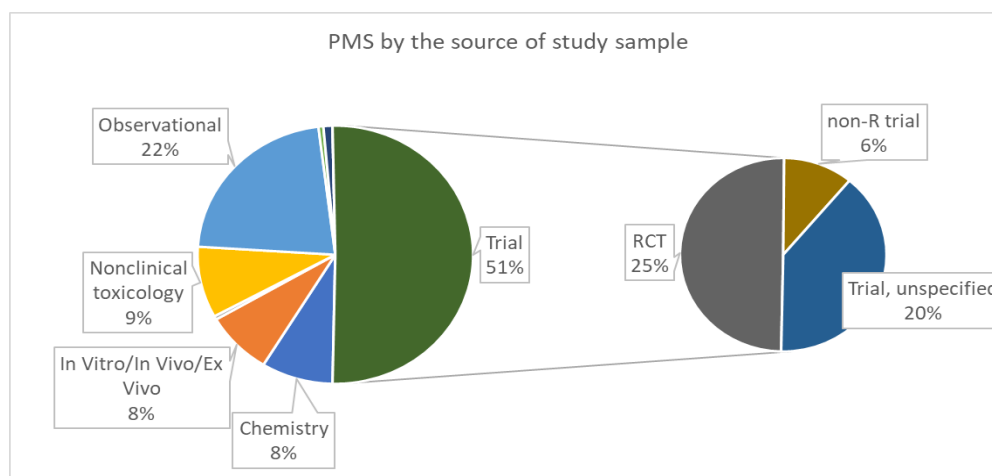


**Figure B-20. PMR/PMC status by establishment year**



**Figure B-21. The status of PMS established between July 2008 and December 2010 (sample size = 658)**

Notes: figure (a) all PMR/PMCs in the sample; figure (b) Fulfilled PMR/PMCs in the sample, by study design; figure (c) Fulfilled PMR/PMCs in the sample, by requirement vs. commitment, and by expedited vs. non-expedited



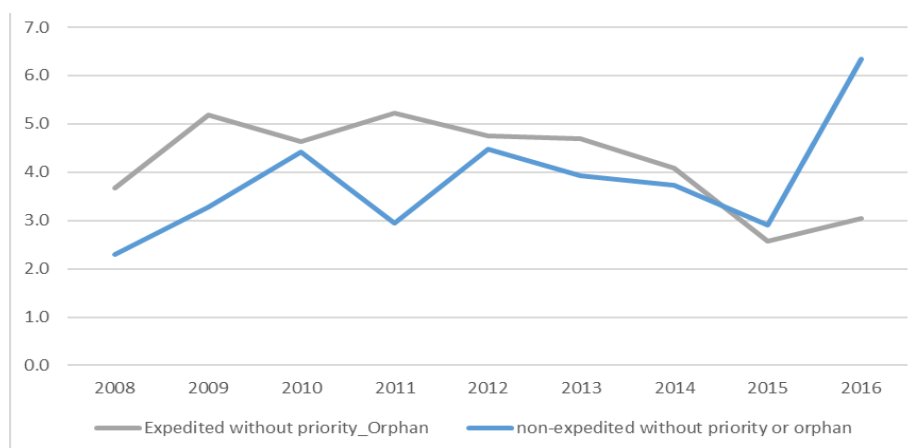
**Figure B-22. PMR/PMCs by the source of sample**

Notes: by the source of sample, 51% of postmarketing studies were based on clinical trial data and half of them are data from randomized trials. In Figure 1-12 in Section 1.4.5, we observed that 42% of studies were clinical trials, but the percentage increased to 51% when including other study designs using samples from clinical trials. This means that 16% of non-clinical-trials use samples from clinical trials—mostly “trial follow-ups” and “analysis” studies (100% of trial follow-ups are based on clinical trial sample, and 71% of analysis studies are based on clinical trial data).

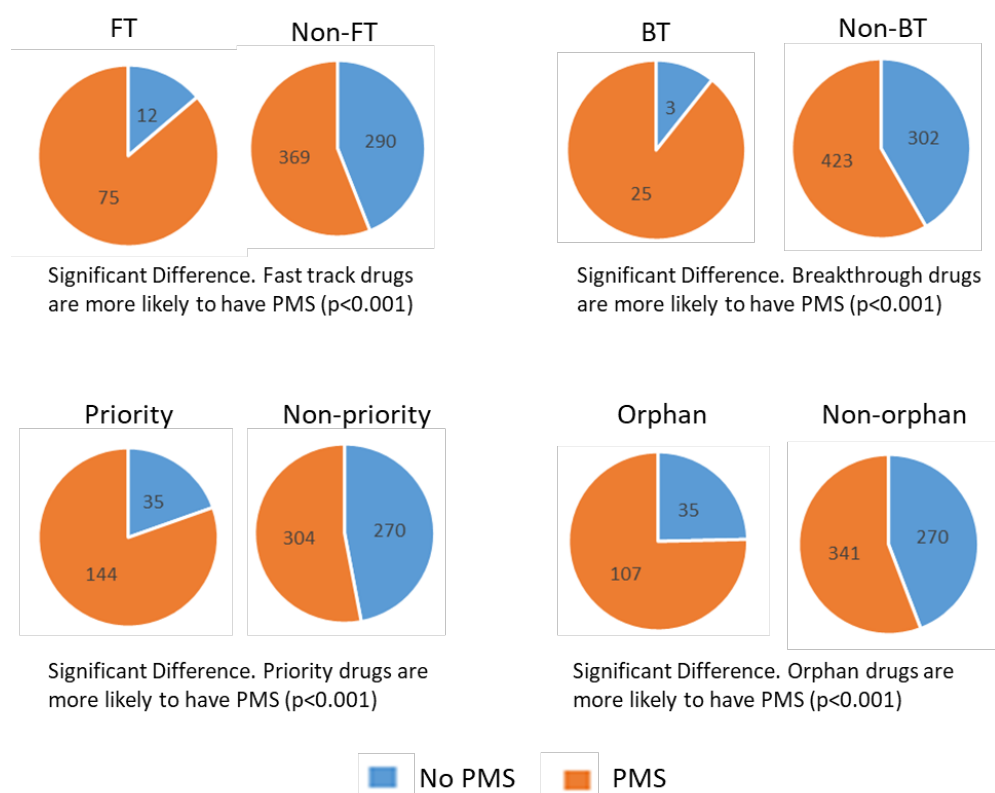
	RCT	non-R trial	Trial, unspecified	Trial follow-up	Obs	In Vitro/In Vivo/Ex Vivo	Nonclinical toxicology	Analysis	Pooled analysis	Chemistry	Other	Un-determined
Safety	●	●	●	●	●	●	●	●	●	-	●	●
Efficacy	●	●	●	●	●	-	-	●	-	-	-	●
Confirmatory	●	●	●	●	●	-	-	●	-	-	-	-
DDI	●	●	●	-	-	●	-	●	-	-	-	-
Dose	●	●	●	-	-	●	●	●	-	-	-	-
Immunogenicity	●	●	●	-	●	●	-	●	●	-	●	●
Microbiology	-	●	●	-	●	●	-	●	-	-	-	-
Biopharmaceutics	●	-	●	-	-	-	-	●	-	-	-	●
Multipurpose	●	●	●	●	●	-	-	●	-	-	●	●
Product	-	-	-	-	-	-	-	-	-	●	●	-
Utilization	-	-	●	-	●	-	-	-	-	-	●	-
Other - pharmacology	●	●	●	-	-	-	-	●	●	-	●	●
Other	●	●	-	-	●	●	●	●	-	-	●	●
Undetermined	-	-	●	●	-	●	-	●	-	-	-	-

**Figure B-23. Matrix by study design and study purpose**

Note: The size of circles indicates the number of PMR/PMCs



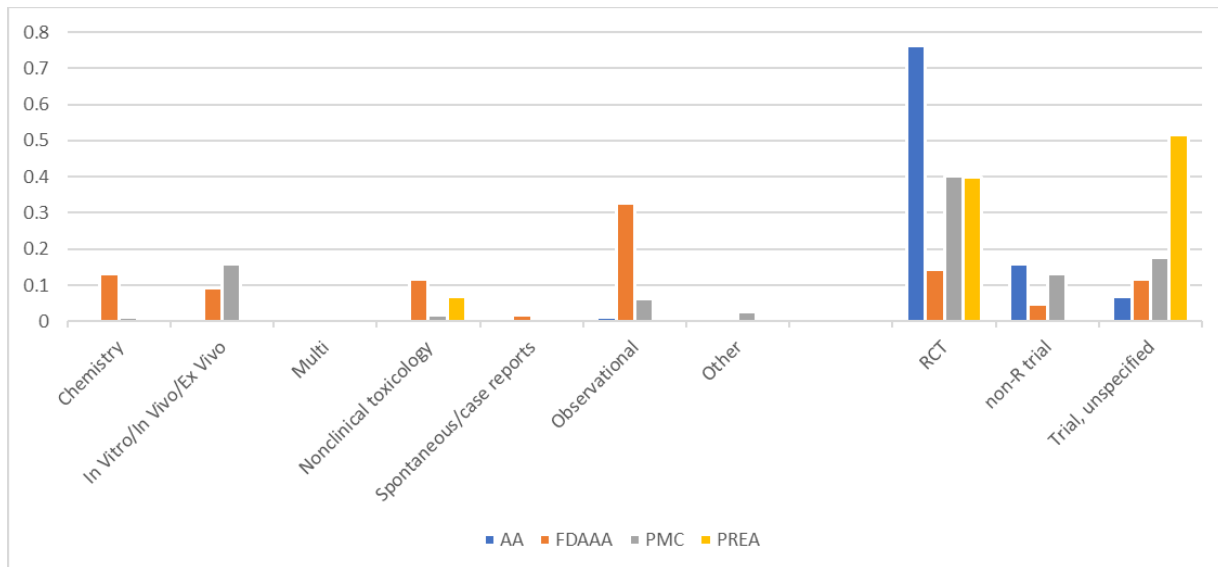
**Figure B-24. The average number of PMS, by expedited or orphan, without Priority review designation**



**Figure B-25. The number of new drug approvals with PMS and without PMS, by expedited or orphan designation**

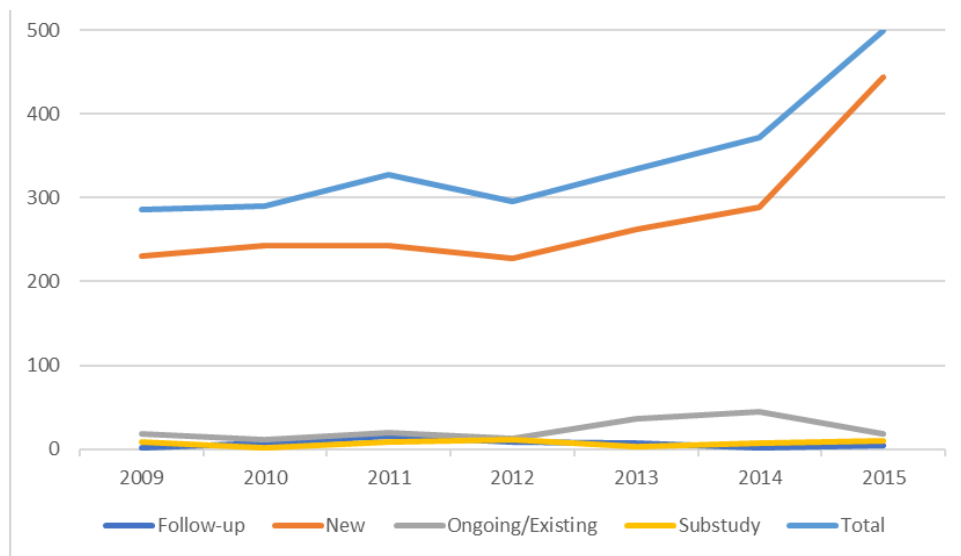
**Notes:**

1. 753 new NDA/BLAs approved between July 2008 and May 2016.
2. The numbers within the pie charts indicate the number of NDA/BLAs.
3. Fast track status for 7 drugs were undetermined (information not available).
4. Accelerated approvals were excluded from the analysis because PMR is mandated when accelerated approvals are granted.

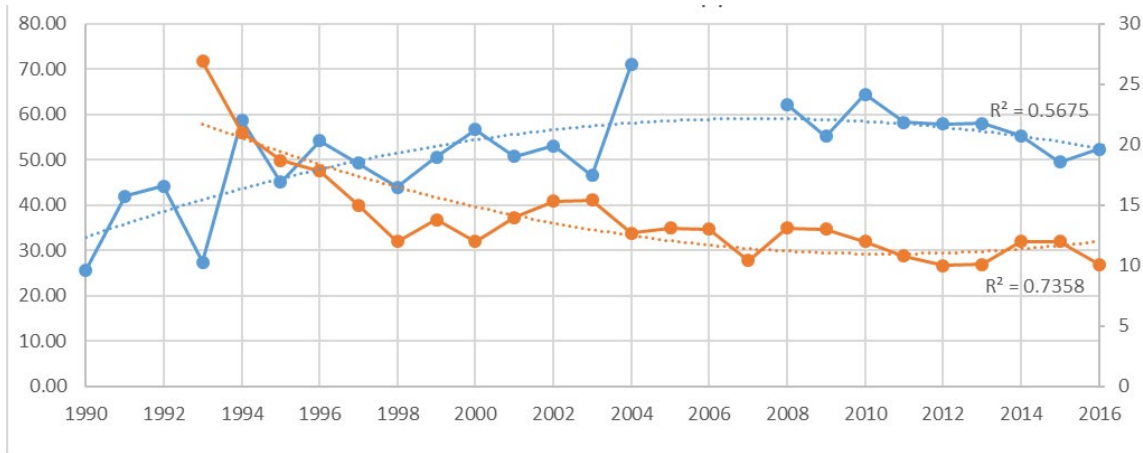


**Figure B-26. Percentage of PMS, the source of sample and PMS type**

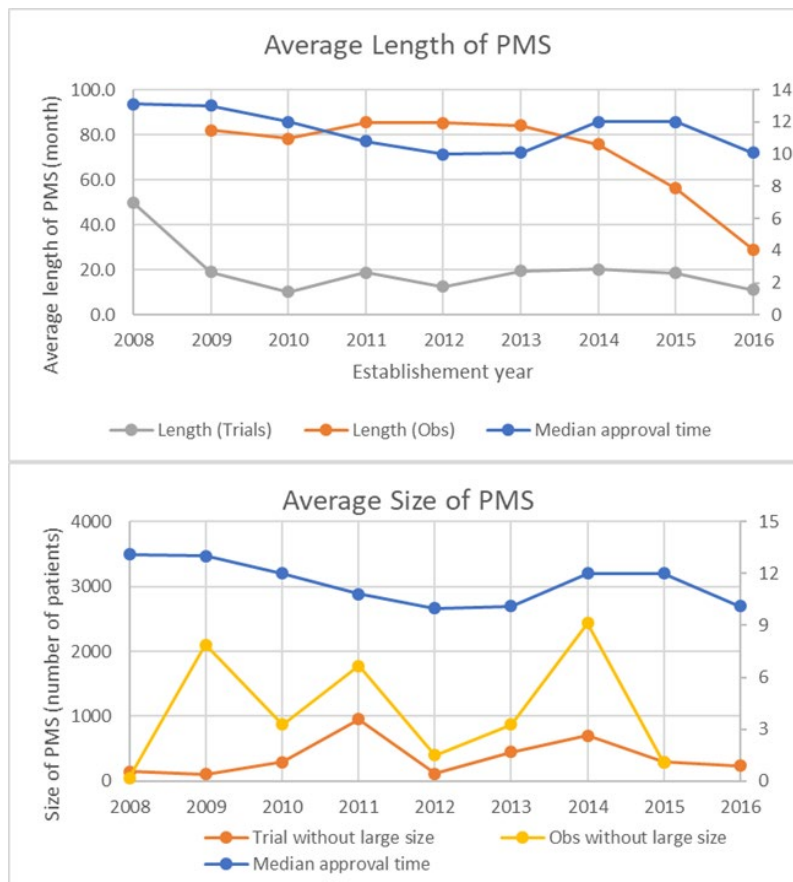
Notes: Y-axis is the percentage of PMS per each types of PMS



**Figure B-27. The number of PMS by PMS categories (2009-2015)**

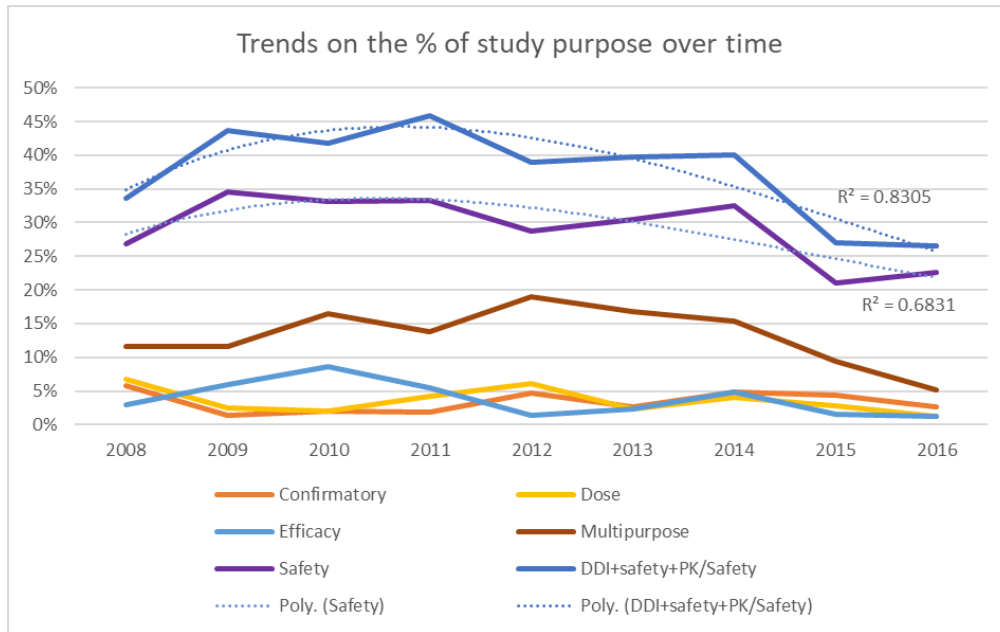


**Figure B-28. Percentage of NDAs with at least one PMR/PMC and Median approval time (standard review)**



**Figure B-29. Average length and size of PMR/PMCs and median approval time (standard review)**

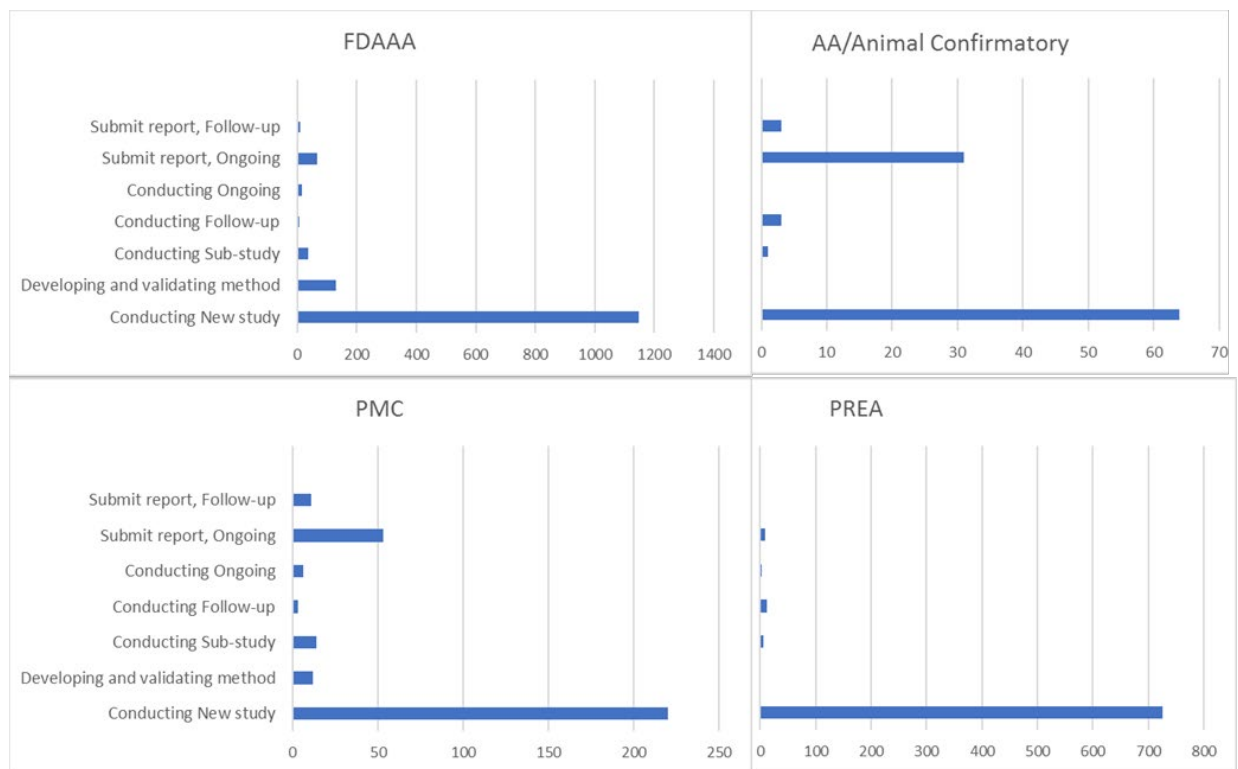




**Figure B-30. Trends on the percentage of study purpose, 2008-2016**

## Appendix C for Study 1: Types of Studies

As explained in Section 1.3.2, I classified PMR/PMCs into 7 categories depending on the nature of the studies. Some studies are all about submitting the final report, data, or additional analysis from existing studies while others are to conduct clinical trials, nonclinical trials, or observational studies. Also, some studies are newly established while others are established as follow-ups or sub-studies. Figure 1-31 below presents the overview of PMR/PMCs by categories and PMR/PMC types (legal statutes).



**Figure C-31. Nature of studies, by PMR/PMC type**

### Notes:

1. These graphs show the number of PMS by categories and by PMR/PMC type
2. Sample size is 2,583: PREA 752, FDAAA 1,410, AA/Animal 102, PMC 319 (the sample doesn't include 232 PMR/PMCs because the classification was undetermined). All 14 animal studies are field studies in case of exposure—all new studies. There was a total of 88 AA studies.
3. Conducting new study: newly established study, Conducting follow-up: newly established follow-up study of trial(s), Conducting sub-study: newly established sub-study under ongoing/existing trials or studies,

Submitting ongoing study: submit the final report, analysis, or data for ongoing/existing studies, Submitting follow-up: submit the final report, analysis, or data for follow-up studies, Submitting sub-study: submit the final report, analysis, or data for sub-studies, and Developing/validating method: developing or validating method or measure.

The majority of postmarketing studies are new studies (89%) without association with existing studies—"conducting new study" category—despite some differences among the study types. All 14 animal studies are field studies that would be conducted in the event of bio terror attack or exposure to acute radiation. Thus, these are all new studies. The overwhelming majority of PREA studies (96%) are newly established PMR/PMCs. The rest 4% are conducting ongoing, follow-up, or sub-study or submitting reports. And, 91% of FDAAA safety studies (1,277 out of 1,410) are new studies and 10% of those new studies were about developing/validating methods (130).

On the other hand, not many AA studies are newly established requirements. Out of 88 AA studies, 57% were newly established and 35% were already ongoing (at least protocols approved). It is because many phase 3 confirmatory trials are already begun at the time of approval. For postmarketing commitments, 87 out 319 commitments (27%) were about submitting reports or conducting ongoing or follow-up.

Postmarketing study examples by study categories:

- Conducting new study: A 26-week randomized, controlled trial comparing once weekly Trulicity (dulaglutide), 0.75 mg and 1.5 mg, with insulin glargine on glycemic control in patients with type 2 diabetes mellitus and moderate or severe renal impairment, with a 26-week controlled extension.

- Conducting follow-up: A long-term follow-up study to evaluate long-term efficacy and immunogenicity outcomes in a subpopulation of patients in LOTS and LOTS Extension Studies whose response to Lumizyme (alglucosidase alfa) is associated with substantial improvement over baseline in the 6 minute walk test (6MWT) results. This study will be conducted as a sub-study within the ongoing Pompe Registry.
- Conducting sub-study: A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.
- Conducting on-going/existing study: Submit integrated analyses for genotypic and phenotypic resistance for studies AI463048, AI463050, AI463085, AI463901, AI463110, and AI463111, and integrated phenotypic resistance analyses for studies AI463028 and AI463189 in SAS format. The virology data should be submitted following the guidance format.
- Submitting report/data, ongoing: Submit a final report for ongoing observational study M13-102, "A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy in Subjects Who Participated in

Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection."

- Submitting report/data, follow-up: Submit the per protocol overall survival follow-up (data cut-off date will be at least 5 years from the date of the last patient randomized) for Trial SSGXVIII/AIO entitled "Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk for recurrence (SSG XVIII/AIO)". Updated OS results including datasets will be provided as an addendum to the full clinical trial report (dated 27-June-2011).
- Developing/validating methods/measures: An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

## **2.0 Study 2: Value of postmarketing studies: How Does FDA Utilize Drug Information Acquired Through Postmarketing Studies?**

### **Abstract**

The importance of postmarketing information was reflected in the passage of the Food and Drug Administration Amendment Act (FDAAA) of 2007 that authorized Food and Drug Administration (FDA) to require drug sponsors to conduct postmarketing safety studies. Postmarketing studies play important roles in reducing uncertainties and the number of postmarketing studies has increased over the past decades. At the same time, the drug industry claims that the cost of postmarketing studies is a burden. Yet, we know little about the value of postmarketing studies. This paper aims to assess the value of postmarketing studies with respect to public health impact as measured by changes in drug labeling. This requires an examination of regulatory actions taken by the FDA on the basis of study findings. This study looks at market status changes (discontinuations and withdrawals), drug label changes, and risk evaluation and management strategies (REMS) assignments that result from the findings of postmarketing studies. The study cohort is 110 postmarketing studies that were established for drug approvals granted in 2008. This study found that withdrawal or discontinuation of a drug resulting from postmarketing studies is rare and a half of fulfilled postmarketing studies resulted in label changes.

## 2.1 Introduction

In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), which authorized the Food and Drug Administration (FDA) to require certain postmarketing studies and clinical trials<sup>71</sup> of prescription drugs and mandated adherence to study deadlines. FDAAA was a significant step to provide more information about safety and effectiveness of drugs after approval, but only part of a longer-term trend to increase the use of postmarketing studies (PMS). The increasing trend of postmarketing studies is accompanied with the United States drug regulatory paradigm shift from approval-oriented approach to life-cycle management.

Recognizing the need for life-cycle management of drugs, the move towards postmarketing studies allows FDA to gather more new information on drugs in the real-world setting. But, it also brings costs. According to Robert R. Ruffolo in 2003<sup>72</sup>, when he was president of research and development of Wyeth Pharmaceuticals and senior VP of Wyeth,

*“Requests for additional studies postmarketing have become nearly automatic. These studies account for 26% of funding allotted for all preapproval and postmarketing clinical studies, which is money that becomes unavailable for funding the development of innovative new drugs. This contributes to the decrease in productivity that has become so apparent. A good amount of our resources are*

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<sup>71</sup> FDAAA makes a new distinction between “study” and “clinical trial.” Previous laws, regulations, and practice generally used the terms studies and trials interchangeably. For example, section 506B of the Act (21 U.S.C. 356b) uses “studies” to describe the postmarketing commitments (PMCs) that must be reported annually, including clinical trials. Hereinafter, I use the term “study” for both clinical trials and non-trial studies in this document unless the distinction is necessary. Thus, postmarketing studies (PMS) include postmarketing requirements (PMR) and postmarketing commitments (PMC) in trial, observational, and non-clinical settings.

<sup>72</sup> <http://www.pharmavoice.com/article/220/>

*diverted away from new drugs to study drugs that have already been determined to be safe and effective. The approval, which a company has been waiting for many years, may be held over its head in exchange for agreeing to do a study that it doesn't want to do”*

This study aims to examine FDA’s use of information from postmarketing studies to shed light on the value of postmarketing studies in relation to public health. Monetizing the health impact of postmarketing studies is out of the scope of this project. Instead, this study requires a close look at regulatory actions taken by the FDA after postmarketing studies are fulfilled. Regulatory actions include market status changes (discontinuations and withdrawals), label changes, and risk evaluation and management strategies (REMS) assignments that result from the findings of postmarketing studies. (See Table 2-1) These changes in drug information are assumed here to result in public health benefits although we realize that the connections are not always clear.

**Table 2-1. FDA’s postmarketing regulatory actions that can result from postmarketing studies**

Type of action	Sub-categories
Market Status Change	Withdrawal, Discontinuation
Risk Mitigation	Risk Evaluation and Mitigation Strategy (REMS)
Drug Label Change	Black boxed warnings (located at the top of drug labels) Indications and Usage (section 1) Dosage and administration (section 2) Contraindications (section 4) Warnings and precautions (section 5) Adverse reactions (section 6) Drug interactions (section 7) Use in specific populations (section 8)

Note: FDA uses the terms “labeling change” and “labeling revision” interchangeably. Hereinafter, the two terms are used interchangeably.



This paper aims to contribute in three ways.

1. First, I will investigate the association between postmarketing studies and label changes by comparing drugs with postmarketing studies and drugs without postmarketing studies. And, I will look at black box warnings and indication changes in order to compare safety label changes and efficacy label changes resulted from postmarketing studies.
2. I will examine the possibility of other regulatory actions than label changes: market status change and further risk management assignment.
3. Finally, I will develop a statistical model to estimate the probability of label changes by characteristics of studies and drugs, including all types of drug approvals granted in 2008: new and supplemental approvals, new drug applications (NDAs) and biologic license applications (BLAs), new molecular entities (NMEs) and non-NMEs, and all therapeutic drug class. Given the lack of research about the use of FDA's postmarketing requirements (PMRs) and commitments (PMCs), there may be opportunities to enhance FDA's use of information that could be translated into public health benefit.

## **2.2 Background and Literature**

### **2.2.1 Background**

#### **2.2.1.1 Establishment and Process of Postmarketing Studies**

Once approved, sometimes additional studies are conducted following the approval of a new drug application (NDA) or biologic license application (BLA) by the FDA, “during general

use of the drug by medical practitioners” (Lipsky and Sharp, 2001). These studies are referred to as postmarketing studies (Lipsky and Sharp, 2001) and these studies are funded by sponsors.

Postmarketing study is a term used to describe all research activities after the approval of a NDA or BLA<sup>73</sup> by the FDA. A postmarketing requirement is a study that the FDA mandates as a condition for approval as defined in section 901 of the 2007 FDAAA<sup>74</sup>. On the other hand, a study that is not required by statute might be conducted because a sponsor and the FDA agree, in writing, that such study should be conducted. This is a postmarketing commitment. See Table 2-2 for types and legal statutes of PMRs and PMCs.

**Table 2-2. Types of Postmarketing Studies and Statutes**

	Requirement (PMR)	Commitment (PMC)
Laws/Rules	<ul style="list-style-type: none"> <li>• Animal Efficacy: 1999 Animal Rules<sup>75</sup></li> <li>• Accelerated Approval: 1992 Accelerated Rules<sup>76</sup></li> <li>• Pediatric Studies: 2003 PREA<sup>77</sup></li> <li>• Safety studies<sup>78</sup>: 2007 FDAAA<sup>79</sup></li> </ul>	1997 FDAMA <sup>80</sup> (Agreed-upon postmarketing studies that do not meet the statutory criteria for PMRs)
Enforcement	Charges under section 505 of the Act Misbranding charges (section 502(z)) Civil monetary penalties (section 303(f))	No enforcement

[Acronyms] PREA = Pediatric Research Equity Act, FDAAA = Food and Drug Administration Amendment Act, FDAMA = Food and Drug Administration Modernization Act

<sup>73</sup> Conventional drugs are chemically synthesized, and biologics are manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are large, complex molecules or mixtures of molecules. Hereinafter, “drugs” refer to both conventional drugs and biologics regulated by CDER. CBER biologics are not included.

<sup>74</sup> Section 901 of the 2007 FDAAA created section 505(o) of the FD&C Act that states that the FDA can mandate PMRs in certain situations such as to confirm clinical benefit when a drug has been given “accelerated approval,” to assess risk associated with the drug, or to examine pediatric populations.

<sup>75</sup> 21 CFR 314.610(b)(1), Subpart I (drugs); 21 CFR 601.91(b)(1), Subpart H (biologics)

<sup>76</sup> 21 CFR 314.510, Subpart H (drugs); 21 CFR 601.41, Subpart E (biologics)

<sup>77</sup> 21 CFR 314.55(b) (drugs); 21 CFR 601.27(b) (biologics)

<sup>78</sup> Section 505(o) of the Act states that postmarketing studies and clinical trials may be required for any or all of three purposes related to risk:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

<sup>79</sup> Section 505(o)(3) of the FDCA

<sup>80</sup> 21 CFR 312.85

Table 2-1 shows the types of postmarketing requirements by legal statutes. The postmarketing studies that can be required under FDAAA join the types of postmarketing studies that FDA could require before FDAAA. Before FDAAA, FDA could require the following postmarketing studies:

- Postmarketing studies to demonstrate clinical benefit for drugs approved under the accelerated approval requirements in 21 CFR 314.510 and 21 CFR 601.41 (Confirmatory studies for accelerated approval)
- Deferred pediatric studies (21 CFR 314.55(b) and 601.27(b)), where studies are required under the Pediatric Research Equity Act (PREA)
- Postmarketing studies to demonstrate safety and efficacy in humans that must be conducted at the time of use of products approved under the Animal Efficacy Rule (21 CFR 314.610(b)(1) and 601.91(b)(1)) (Animal studies)

Under FDAAA, postmarketing studies also can be required to:

- Assess a known serious risk related to the use of the drug
- Assess signals of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Another change brought by FDAAA is the distinction between postmarketing requirements (PMRs) and commitments (PMCs). In 1997, when the Food and Drug Administration Modernization Act (FDAMA) was passed, the Modernization Act required sponsors of approved drugs to report to FDA on the progress of their postmarketing commitments, which was defined

to include required studies—confirmatory studies for accelerated approvals, PREA studies, and animal studies—and agreed-upon commitments. Now, under the FDAAA of 2007, commitments and requirements are treated differently because section 505 created safety requirements—some of them were previously commitments.

The PMR/PMC development process typically occurs during the NDA/BLA review phase. According to Booz Allen Hamilton (2008), in general, “the PMC development process (note that the study examined only PMCs) is initiated when a data gap or issue is identified, which typically happens early in the review process.”<sup>81</sup> Once an issue was identified, FDA discussed the PMC with the sponsors<sup>82</sup> and the PMC is documented in the action letter (approval letter<sup>83</sup>), the Booz Allen reported (2008). Then, the FDA tracks and reviews PMC activities: the Agency reviews sponsor-submitted materials and communicates with sponsors as needed.

After the final report submission, the FDA decides whether a PMR/PMC is fulfilled. According to the FDA industry guidance<sup>84</sup>, if the FDA concludes that the study commitment has been met, it will consider the commitment satisfied and will notify sponsors that the commitment is fulfilled. “If a study was completed but failed to satisfy the purpose of the study, but would still provide useful information and can be addressed through a study of modified design, the Agency

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<sup>81</sup> BAH (2008) says that “82% of issues were identified after application submission and before the end of the review phase”

<sup>82</sup> BAH (2008) says that “once an issue was identified, FDA occasionally notified the sponsor of the issue before making the decision to address it as a PMC; however, in many cases FDA did not discuss the gap in product information with the sponsor until after the PMC decision point. The PMC decision point occurred most often in the review phase (59%), but also occasionally in the action phase (23%). Despite this relatively early PMC decision point, sponsors were more likely to be notified of the PMC late in the review, during the action phase (65%), than in the review phase (33%).”

<sup>83</sup> “An action letter is a letter to an applicant that is issued after the complete review of a filed application..... FDA issued an action letter (not approvable, approvable or approval letter) after a complete review of the application. If not an approval, the action letter contained a complete list of deficiencies in the application and completed the review cycle for the application. The next review cycle (resubmission) began when the agency receive a complete response to all deficiencies listed in the letter.”

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172134.pdf>

<sup>84</sup> <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>

may release the original commitment and establish a new PMR/PMC and schedule. If the FDA agrees that the failed study is no longer feasible or would not provide useful information, the FDA may release the PMR/PMC. If a study is terminated and the FDA determines is still feasible, would yield useful information, and can be addressed through a study of modified design, the Agency may release the original study and establish a new postmarketing study and schedule. If the FDA agrees the terminated study is no longer feasible or would not provide useful information, the FDA may release the study.” (FDA, 2012) A description on each PMR/PMC status is provided in Table 2-4 in Section 2.3.2.

And, finally, the FDA reviews a supplemental application (for labeling revision) if the application is accompanied with the final report. The FDA manual (MAPP 6010.2)<sup>85</sup> says that “a final report submitted as a supplemental application will be reviewed according to established review times for supplements. A final report submitted without a supplemental filing should be reviewed within 1 year of receipt.” If a supplemental application for labeling revision was not accompanied, the FDA or sponsor could still change the drug label and post the findings from postmarketing studies to communicate with patients and doctors (Drug Safety Communications). FDA also could withdraw approval or require REMS.

On a separate note, PREA studies are recognized as “fulfilled” when labeling revision application is accompanied with the final report. It is because the purpose of PREA is to update drug labels for children. The FDA usually doesn’t change the status of a PREA study unless the

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<sup>85</sup> Manual Of Policies And Procedures, MAPP 6010.2, Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments, CDER/FDA  
<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM174552.pdf>

sponsor submits the proposed labeling revision because the purpose of PREA is to label drugs for children adequately.<sup>86</sup>

### **2.2.1.2 FDA drug regulation policy changes**

For many years, discussions of innovation and regulation of drugs have focused on a tension between efforts at faster approval and efforts at safer approval. This tension can be framed as tight preapproval requirements and loose postmarketing regulation (IOM, 2007; Avorn, 2004). Requiring strong evidence of safety and efficacy of a drug before its approval could prevent harmful or ineffective drugs from being marketed and thus save lives and costs. But it could also delay access to drugs for patients who might benefit from a potentially life-saving drug and limit a firm's resources to develop new drugs. Such trade-offs may have driven the FDA and policymakers to respond to the accumulation of failures in one side by swinging to the other side.

During the 1970s, drug regulation debates centered on the “drug lag” issue. Critics of the FDA argued that the implementation of the 1962 Amendments to the FD&C Act reduced the incentive of firms to develop innovative drugs and limited treatment options for patients who desperately need medicines (See Wardell; Peltzman; Kaitin, Lasagna, and Richard). Many drugs

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<sup>86</sup> For example, on PMR/PMC status description about KEPPRA (LEVETIRACETAM)100MG/ML INJECTION (NDA #21872), the agency noted, “The final study report was submitted to FDA on January 31, 2011. However, UCB has not yet submitted the report of this required pediatric postmarketing study as a new drug application (NDA) or as a supplement to their approved NDA with the proposed labeling changes they believe are warranted based on the data derived from this study. Because the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) requires this accompanying submission to the PMR final study report, this PMR is therefore considered delayed.”

that were approved in Europe and began saving lives were delayed considerably in the United States.<sup>87 88</sup>

Some drug policy scholars and policymakers advocated that the regulatory system would work better if the FDA placed more emphasis on examining the safety and efficacy of drugs after marketing and on reducing the barriers to the approval itself (Wardell and Lasagna, 1975; Wardell, 1979; Viscusi et al., 2005; Gottlieb, 2016<sup>89</sup>; Becker, 2002).

Another source of delay in the US drug approval is the time required for the FDA's review of drug applications. In this context, critics claimed that the agency's review process took long (Hutt and Merrill, 1980). GAO report (1996) says that the median review time in the US was 23 months while it was 20 months in the UK for 11 drugs approved 1986-1992 (Harvey et al., 1993). According to Carpenter (2004), the median FDA review time for new molecular entities (NMEs) submitted in 1978 was 30.8 months (13 months during 2008-2009).

To some degree, these critiques have contributed to the changes in FDA policy adopted since the 1990s. Measures have been taken to speed drug approval: among the measures taken are

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<sup>87</sup> Sam Peltzman concluded, in his 1974 study, that the new efficacy standards were adding at least two years to a new drug and that the regulators made it difficult for companies to introduce drugs competing with existing drugs. He also argued that the 1962 amendments "did successfully reduce consumers' expenditures on ineffective drugs, but only by reducing consumer access to all new drugs." He said that "the incidence of ineffective new drugs does not appear to have been materially reduced....even if it had been, the pre-1962 waste on ineffective new drugs that might now be prevented appears to have been too small to compensate for the benefits consumers have had to forgo because of reduced drug innovation."

<sup>88</sup> Empirical studies were conducted by Wardell and the CSDD (Kaitin, Lasagna, and Richard). Wardell estimated that 3,700 Americans may have died from less safe drugs because the relatively safe hypnotic drug nitrazepam was not approved until 1971, five years after it was available in the UK. Wardell also argued that Praxolol could save 10,000 lives per year if allowed. The CSDD studied 46 new chemical entities (NCEs) approved in 1985-1986 and found that 71.7% were available on average 5.5 years earlier in foreign markets.

<sup>89</sup> "Expediting the development of these novel and transformative technologies like gene- and cell-based therapies doesn't necessarily mean lowering the standard for approval, as I believe other countries have done. But it does mean having a framework that's crafted to deal with the unique hypothetical risks that these products pose. It means shifting much more of the emphasis on active surveillance as opposed to FDA's historically more binary approach to regulation, that transfers most of the responsibility to the pre-market review process." Scott Gottlieb (2016), <https://www.forbes.com/sites/scottgottlieb/2016/01/12/fda-needs-to-change-how-it-regulates-novel-technologies/#2636756c191e>

accelerated approval, priority review, breakthrough therapy, and fast track<sup>90</sup>. For instance, accelerated approval, officially established in 1992, is an approval path that allows drugs to be marketed based on surrogate markers. Prescription Drug User Fee Act (PDUFA) of 1992 incentivized the FDA to shorten its review time for approval.<sup>91</sup> <sup>92</sup> These expedited drug approvals and the introduction of PDUFA shortened time to approval<sup>93</sup> <sup>94</sup> and increased the role of postmarketing studies and surveillance in managing uncertainty and risk.<sup>95</sup>

In 2002, the reauthorization of PDUFA III “rekindled policy emphasis on drug safety, mandating the FDA to direct risk management guidance for chemical entities and biologics and making it possible for the FDA to dedicate part of the user fees on risk management and post–

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<sup>90</sup> Orphan drug designation qualifies the sponsor for development incentives of the orphan drug, including tax credits for qualified clinical testing, patent exclusivity, and fee waiver for PDUFA. Orphan drugs do not automatically qualify for expedited approval.

<sup>91</sup> “It (PDUFA) has been a key to ending major problems with unpredictable and slow review and approval of new drug applications. It has provided funds to eliminate or even reversed the so-called “drug lag” attributed to inadequate staff and computer resources. Americans now get access to more new medicines faster than patients in other countries, while prior to PDUFA, American patients waited for FDA to act long after new drugs were available in Europe.” FDA acknowledged PDUFA as a tool to reduce the drug lag. Source: FDA. White Paper, Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications. (No publication date, but it seems published in 2005 or 2006)

<sup>92</sup> The Orphan Drug Act of 1983 is also regarded as an effective policy to reduce the drug lag in orphan products in the US (Grabowski and Wang, 2006).

<sup>93</sup> The median FDA review time for NMEs has decreased over time: from 30.8 months in 1978 to 18 months in 1994 to 13 months during 2008-2009 (Carpenter, 2004). And, Downing et al. (2017) showed that the median total review time is shorter in the US than in Europe: 306 days at the FDA (approved 170 new therapeutic agents) and 383 days at the EMA (approved 144 new therapeutic agents). Downing et al. (2012) showed that the median length of time for completion of the first review was 303 days (interquartile range, 185 to 372) for applications approved by the FDA, 366 days (interquartile range, 310 to 445) for those approved by the EMA, and 352 days (interquartile range, 255 to 420) for those approved by Health Canada ( $P < 0.001$  for the comparison across the three agencies).

<sup>94</sup> Roberts et al. (2011) found that for cancer drugs, review times were even more abbreviated—by about 6 months in the United States. All of the drugs that were approved by both the FDA and EMA were available sooner to patients in the United States, in part because of consistently shorter review times at the FDA. Furthermore, during the same period of time, the FDA approved a larger number of cancer drugs than the EMA (35 vs. 29, respectively)

<sup>95</sup> Carpenter and his colleagues (2008) said, “After 1992, when the PDUFA was passed and deadlines for drug approvals were introduced, FDA drug approval decisions were concentrated in the 2 months just before the deadlines.... approvals made in the last 2 months before a deadline were more likely to be associated with subsequent safety problems....As noted in two major reports of deficits in the FDA's capacity for postmarketing safety surveillance, ongoing assessments of drug risk are not conducted systematically....[but the later data] showed no increase in problems after the PDUFA....Approvals earlier in the review cycle were not inherently more likely to lead to postmarketing safety problems; it appears to be the deadline, not the speed of approval, that explains the difference in the risk of such problems.”



market surveillance.” (Slomiany et al., 2015) As implementation of this act, in 2005, the FDA published guidance for risk minimization action plans (RiskMAPS). In 2007, the Congress expanded RiskMAPS and it became REMS.

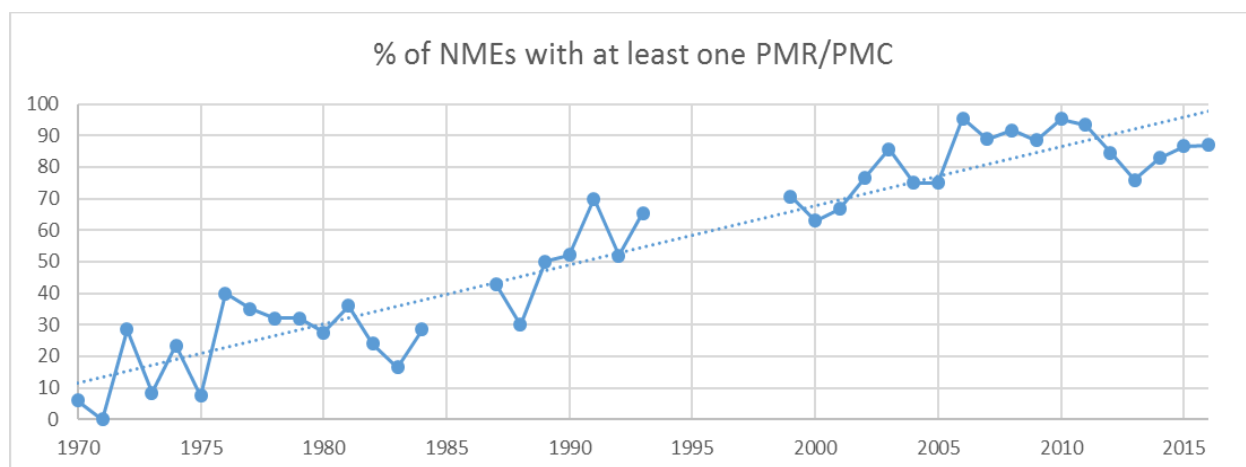
At the same time, in the early 2000s, there was a growing concern about drug safety among the public, too, fueled by the Redux saga and Vioxx withdrawal (Psatsy, the Vioxx hearing, 2004; Wolfe and Sasich, FDA hearing, 2002; Fontanarosa et al., 2004; Brewer and Colditz, 1999). These withdrawals stoked fears in two ways. First, could the same agency that approved new drugs be relied on to monitor postmarketing reports for signs that reviewers had made a mistake (Fontanarosa et al., 2004)? Second, the problems with Vioxx demonstrated that spontaneous reporting strategies alone cannot elucidate the safety profiles of drugs (Brewer and Colditz, 1999). Consequently, these concerns made postmarketing studies more crucial.

In addition to the critiques and factors that contributed to more emphasis on postmarketing studies, issues with preapproval studies and study designs add to justification of the rationale for requirements and commitments after approval. Preapproval studies are necessarily limited in size and tend to be narrow compared to postmarketing studies: preapproval trials generally seek subjects who are as homogenous as possible, in order to reduce unexplained variability in the outcome variables and increase the probability of detecting a difference between the study groups (Strom, et al., 2012). The increased sample size available after marketing also permits a more precise determination of the correct dose to be used (Cross et al., 2002; Heerdink, et al., 2002; Peck, 2003; Temple, 2003).<sup>96</sup>

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<sup>96</sup> Let us say that drug A resulted in an increase of 1 in 1000 deaths per year among patients. If the drug was only used among 1,000 people every year for a specific, relatively rare disease this might be a minor problem. But when the drug is widely used in a population where the average number of deaths per year was 1, 5, or 10 per 1,000 patients, the sample size necessary to identify an increase in 1%, 2%, or 3% of the deaths is very substantial and very difficult to find. (Kuller, interview)

Since the 1970s, more drugs have been approved with postmarketing requirements and/or commitments. Figure 2-1 below exhibits the percentage of new molecular entities (NMEs)<sup>97</sup> with at least one postmarketing study over time since 1970. Despite some fluctuations, it clearly shows an upward trend: more NMEs are approved with at least one postmarketing study. Between 1970 and 1975, the percentage of new chemical entities (NCEs)<sup>98</sup> with a postmarketing study averaged 12%. Since 2008, on average, 87% of NMEs have been approved with at least one postmarketing study.



**Figure 2-1. Time trend: Percentage of NMEs with at least one postmarketing study (1970-2016)**

Note: No dataset is available for NMEs with PMR/PMCs over an extended period of time, and therefore this graph was derived from three different data source: (1) Mattison and Richard data (NCEs approved during 1970-1984), (2) OIG data (NMEs approved during 1987-1993), and (3) author's own data (NMEs approved during 1999-2015)

Table 2-3 provides the number of postmarketing studies established from 2009 to 2015.

Note that these numbers include all postmarketing requirements and commitments established for

<sup>97</sup> An NME is a drug that contains an active moiety that has never been approved by the FDA or marketed in the U.S.

<sup>98</sup> An NCE is a drug that contains no active moiety that has been approved by FDA in any other application submitted under FDC Act § 505(b). FDA's classification of a drug as an NME for review purposes is distinct from FDA's determination of whether a drug product is an NCE within the meaning of the FD&C Act. Although their definitions are different, they are very similar in terms of characteristic of "newness."

all drug approvals by the Center for Drug Evaluation and Research (CDER). On average, 86% of the postmarketing studies during this period were required while 14% were negotiated commitments. Fifty-seven percent of the requirements were FDAAA safety requirements. The other requirements included confirmatory studies for accelerated approval (4% on average) and pediatric studies (39% on average).

**Table 2-3. Number of PMR/PMCs established by CDER, FDA (2009-2015)**

Approval	2009	2010	2011	2012	2013	2014	2015	Total
Accelerated	4	6	6	11	10	22	15	74 (4%)
FDAAA	143	139	159	150	191	169	327	1,278 (63%)
PREA	92	90	87	94	91	129	106	689 (34%)
<b>Requirements (PMR)</b>	<b>239</b>	<b>235</b>	<b>252</b>	<b>255</b>	<b>292</b>	<b>320</b>	<b>448</b>	<b>2,041 (85%)</b>
<b>Commitments (PMC)</b>	<b>47</b>	<b>55</b>	<b>75</b>	<b>35</b>	<b>43</b>	<b>52</b>	<b>43</b>	<b>350 (15%)</b>
Total	286	290	327	290	335	372	491	2,391

Note: PMR = Accelerated + FDAAA + PREA. Animal Efficacy PMR is not included (<1%)

However, the growth in postmarketing studies has stoked some controversies.<sup>99</sup> Some say that PMR/PMCs have gone too far and share concerns on the increasing cost of clinical research (Sertkaya et al., 2014) because rising cost may make the industry less willing to take chances on novel drugs (Collier, 2009). Here, the underlying assumption is that having the postmarketing study option would not necessarily guarantee drug approval (if there is a trade-off between postmarketing studies and drug approval, the cost of postmarketing studies may be less than the cost of delaying the approval). Pharmaceutical industry indicated that the rationale for some

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<sup>99</sup> On another account of policy issues related to postmarketing studies, one might argue that the FDA faces problems of protecting the public for almost absolute safety. No single regulatory system can guarantee absolute safety or effectiveness. This is an impossible task, but the public expects nearly absolute safety. For example, in their book *Perspectives on Risk and Regulation: The FDA at 100*, Daemmerich and Radin (2007) wrote “During the century since the passage of the 1906 Federal Food and Drug Act the public has come to expect nearly absolute safety when consuming the products of science-based firms.” And, FDA’s own credibility may be shrunk when approving bad drugs and when postmarketing regulation fails to ensure public health. The Agency’s regulation power may depend on its credibility (in other words, reputation) and drug regulatory effect may be at stake if the agency reputation decreases (Carpenter, 2014; Carpenter and Krause, 2014).

postmarketing studies was unclear and had questionable public health benefit (CSDD, 2007; BAH, 2009).

Although how postmarketing studies impact drug development capacity requires a closer look, there are reasons for concern. Postmarketing studies and trials can be burdensome for small and mid-size pharmaceutical and biomedical firms, and this could result in decrease in R&D for drug innovation. In the 2008 BAH report, those sponsors who recognized that PMCs “did impact R&D noted having limited resources and that any research activity necessarily impacted the amount of R&D for new products.”

### **2.2.2 Literature**

In this study, I will build on prior studies conducted by Booz Allen Hamilton (BAH), a consulting firm, in 2008 (FDA-sponsored study), the Tufts Center for the Study of the Study of Drug Development (CSDD) study in 2007, and Fan et al. in 2016 (the authors are FDA staff).

The BAH study interviewed FDA staff to examine how many postmarketing studies resulted in label changes—all commitments associated with approvals between FY 2003 and FY 2005. And, Fan et al. studied 40 transporter-related<sup>100</sup> postmarketing requirement (PMR) and commitment (PMC) studies between January 1999 and May 2015 by reviewing public and FDA internal review documents. The CSDD surveyed drug firms to find out what they thought about the value of 61 postmarketing studies for 34 products approved during 1998-2005.

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<sup>100</sup> Membrane transport protein (or simply transporter) facilitates the transport of molecules across a biological membrane. (NIH definition, D12.776.157.530) “The importance of evaluating transporter-mediated drug–drug interactions (DDIs) during drug development and regulatory review has been highlighted in several publications and scientific meetings, such as the U.S. Food and Drug Administration's (FDA's) draft DDI guidance in 2006.” (Fan et al., 2016)

These studies have looked at some of these issues. In this section, I review the literature on the following topics: (1) establishment of PMR/PMCs; (2) fulfillment of PMR/PMCs and expedited approval; (3) use of information from PMR/PMCs; (4) sources of evidence for regulatory actions; and (5) other views on the value of PMR/PMCs.

### **2.2.2.1 PMR/PMCs for expedited approvals and fulfillment of PMR/PMCs**

The FDA contracted with Booz Allen Hamilton<sup>101</sup> for an independent analysis of FDA's procedures in order to improve the process for developing and tracking PMCs. The BAH study (2008) found that drugs with fast approval and more uncertainty—priority review, orphan drug designation, fast track, and novelty (NMEs)—are more likely to have postmarketing studies than drugs without such characteristics.<sup>102 103</sup> The explanation provided by the Booz Allen was twofold: (1) FDA “reviewers take into account the potential benefit of a drug when determining whether an issue can be resolved post-approval”; and (2) novel drugs “are likely to have more unknowns, which would also explain the greater number of issues to resolve in the postmarketing phase.” A more recent study by Moore and Furberg (2014) found that “expedited reviews were approved more rapidly.... but considerably fewer patients were studied prior to approval, and many safety questions remained unanswered.”<sup>104</sup>

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<sup>101</sup> The BAH study (2008) analyzed postmarketing commitments associated with new drug applications, biologics applications, and supplements approved during FY2002-05. They excluded studies that were required such as those for accelerated approvals.

<sup>102</sup> This implies that those expedited drugs have bigger potential risk than traditional review drugs and, if so, expedited drugs would be more likely to have requirements rather than commitments compared to traditional review drugs after the passage of FDAAA in 2007. See Figure 2-18 in Appendix D.

<sup>103</sup> This is supported by a 2006 study conducted by the Department of Health and Human Services Office of Inspector General (OIG) that examined postmarketing studies associated with new drug applications approved during FY1990-2004. The OIG study confirmed that the percentage of NDAs with at least one postmarketing commitment had increased since 1990 and that NMEs were associated with more commitments than non-NMEs.

<sup>104</sup> Efficacy testing in the drugs with accelerated approvals was conducted on less than 1/5 of the median number of patients than standard review drugs. Of the 86 PMRs, 26 had been fulfilled more than 4 years after approval.

Several studies have examined how many PMR/PMCs are fulfilled and what efforts FDA has made to enforce the requirements and commitments. In 2010, Booz Allen Hamilton analyzed the status (as of April 2009) of the backlog of 1,551 open PMR/PMCs (not completed as of September 2007). It reported that 16% of the studies were completed and 79% were still open.<sup>105</sup>

<sup>106</sup> Note that definition of each status can be found in Section 2.3.2 Data. FDA's internal policy is to review PMR/PMC final report submissions within 12 months, but workload priorities often compete.

Previously, the U.S. Government Accountability Office (GAO) and OIG uniformly criticized the agency for lack of enforcement and effective information management system (OIG, 1996; OIG, 2006; GAO, 2009). After the continued criticism, the FDA made progress in monitoring and managing PMR/PMCs in the late 2000s. More recent studies (OIG, 2016; Fan et al., 2016) observed that sponsors are making progress toward completing most PMRs according to schedule.

It can be worrisome if more drugs are approved with less clinical testing before approval and quicker review, while postmarketing studies are not enforced. Sertkaya et al. (2014) note that "FDA is justifiably worried about the problematic history of pharmaceutical company promises about post-marketing clinical trials, as some companies have drawn out the process of designing post-market clinical trials for many years." In general, there is a concern about whether FDA's faster approval could increase the potential for previously unrecognized safety issues to appear

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<sup>105</sup> Of the latter, 36% of the studies were submitted, 15% were delayed, 14% were ongoing, 13% were fulfilled, 13% were pending, 3% were released, 1% were terminated, and 5% were unknown/unavailable

<sup>106</sup> In the 2008 study, BAH found that 34% of PMCs were completed (fulfilled or released) and 66% were open (pending, ongoing, submitted, delayed, or terminated). Among a total of 743 PMCs, 224 PMCs (30%) were fulfilled, 28 PMCs (4%) were released, 200 PMCs (27%) were pending, 103 PMCs (14%) were submitted, 96 PMCs (13%) were ongoing, 91 PMCs (12%) were delayed, and 1 PMC was terminated.

once those drugs are widely used and postmarketing studies are not fulfilled (Mostaghim et al., 2017<sup>107</sup>; Darrow et al., 2014; Moore and Furberg, 2014; Carpenter et al., 2008; Carpenter et al., 2012).

#### **2.2.2.2 Use of information from PMR/PMCs**

The BAH study adopted label changes<sup>108</sup> as a proxy measure for the effects of PMCs on public health. From interviews with the FDA review team, Booz Allen found that half (51%) of PMCs led to label changes and that the likelihood of label change varied depending on the type of study<sup>109</sup> and subcategories of study<sup>110</sup>. Microbiology (67%, n=15), clinical efficacy (64%, n=14) and clinical pharmacology (64%, n=39) PMCs were most likely to result in label changes, while immunogenicity<sup>111</sup> (0%, n=7) and non-clinical toxicology (15%, n=13) studies rarely did. And, 52% of clinical safety PMCs resulted in label changes (52%, n=50). BAH further found that certain study subcategories, within each study type, were more likely to result in label changes. For example, adverse events (58%, n=12) and general safety (100%, n=8) subcategories were more

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<sup>107</sup> Mostaghim et al. (2017) concluded that expedited approvals are associated with increased safety labeling revision in the postmarketing setting, particularly for the types of changes representing the highest risk warnings: expedited approvals had a 48% higher rate of changes to boxed warnings and contraindications than non-expedited approvals. “Among the 382 eligible new drugs (1997-2014), 135 (35%) were associated with an expedited development or review pathway, and matches were available for 96 (71%). The matched pairs were associated with a total of 1710 safety related label changes during the study period. Expedited pathway drugs were characterized by a rate of 0.94 safety related label changes for each drug per year, compared with 0.68 safety related label changes per year for non-expedited pathway drugs (rate ratio 1.38, 95% confidence interval 1.25 to 1.52).” The authors used 1:1 matching (using Anatomical Therapeutic Classification) to “create a balanced comparison between drugs associated with expedited development and review programs and those associated with the standard pathway.”

<sup>108</sup> BAH says “a public health benefit was assumed for any PMC that resulted in a label change, since the PMC yielded information that directly impacted the way a product was prescribed and used.” The Booz Allen report notes that the impact of PMCs is not limited to labeling revision. They interviewed FDA reviewers to identify and categorize impacts of PMCs—See Figure 2-12 in Appendix E.

<sup>109</sup> Clinical safety, clinical efficacy, clinical pharmacology, non-clinical toxicology, immunogenicity, and microbiology

<sup>110</sup> Includes PK, PD, DDI, adverse events, education/labeling, special populations, and long-term safety.

<sup>111</sup> Many of immunogenicity PMCs were for assay development to support a clinical trial in a separate postmarketing study, rather than an actual study relating to the product.

likely to result in labeling changes compared to others such as special populations (27%, n=11) and long-term safety (25%, n=4). Note that defining the subcategories was not specified and not all results on subcategories are included in the Booz Allen report.

Despite the agreement between FDA and sponsors when establishing PMCs, half of sponsors indicated that the rationale for some PMCs was unclear and had questionable public health benefit. Sponsors noted that “some studies were already underway or would have been conducted even in the absence of the PMC; thus, the commitment did not produce any data that FDA would not have received without a PMC.” Some sponsors also said that some PMCs appeared to be designed to satisfy an academic interest, rather than a public health concern.<sup>112</sup> These responses from sponsors imply that sponsors agreed to PMCs even when they did not believe in the value of PMCs.

The membrane transporter study (Fan et al., 2016), which was carried out by FDA staff, also looked at label changes. They found that 22 out of 34 fulfilled PMR/PMCs (65%) resulted in labeling updates. The transporter-related studies are important for dose optimization and thus more often included in the updated labeling. The authors also classified the results of PMR/PMCs as “positive” and “negative”<sup>113</sup> based on the conclusions stated in the respective FDA reviews. The data showed that among the 22 studies with labeling revision, 13 had positive results, 7 had negative results, and 2 had mixed results. Among 12 postmarketing studies that did not result in

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<sup>112</sup> “An example, cited by one sponsor, of a PMC believed to satisfy a reviewer’s academic interest was an additional clinical pharmacology study that the sponsor did not feel added to the product’s safety or efficacy profile or enhanced optimal use.” (BAH, 2007)

<sup>113</sup> In clinical trials and studies, “negative” results mean that the studies failed to prove the proposed hypothesis and “positive” results mean the opposite. Fan et al. (2016) defined positive study results and negative study results based on the conclusions stated in the respective FDA reviews (FDA review comments). No further detail was described about how they coded the results of studies.



labeling updates, all showed negative results. This may imply that positive results are more likely to be updated in labels.

### **2.2.2.3 Sources of evidence for regulatory actions**

Postmarketing studies are not the only source of evidence for regulatory actions. The FDA received more than two million spontaneous case reports in 2018 through FDA Adverse Event Reporting System (1.7 million reports on average for the last five years). Among them, more than half of reports (over 1 million, 51%) had serious outcomes such as hospitalization, disability, life-threatening, congenital anomaly, required intervention, etc. And, 18% of the reports resulted in deaths. Each year, the number of reports FDA received increased 18% on average for the last ten years. See Figure 2-14 in Appendix E.

Some researchers looked at the source of information on labeling revisions specifically. The most relevant study was conducted by FDA officials. Lester et al. (2013) reviewed the FDA's internal files on drugs undergoing a 2010 label change—the list of safety label changes was extracted from MedWatch. Evidence sources that resulted in those label changes were categorized as a spontaneous report, clinical trial, pharmacokinetic study, observational study, case report, animal study, or other.

Lester et al. found that there were a total of 407 unique safety issues (safety label changes) among the 371 drugs included in the analysis. The three most common evidence sources that contributed to a label change when analyzed by unique drug (371) were spontaneous reports (55%), clinical trials (14%), and pharmacokinetic studies (9%). (Table 2-12 in Appendix D) They also found that sponsors initiated 58% of safety-related label changes compared to 42% initiated by the FDA. FDA initiated most of the boxed warnings (84% versus 16%) and changes to the

adverse reaction section of the label were more often initiated by the sponsor (78% versus 22%). (Figure 2-6 in Appendix E)<sup>114</sup>

The importance of spontaneous reports in label changes is consistent with the findings from Ishiguro et al. (2012). Ishiguro and her colleagues examined FDA drug safety communications issued from 2007 to 2009. They identified the evidence sources cited in each Drug Safety Communication and following up with relevant FDA/CDER staff. They concluded that the major sources were spontaneous reports (49%), clinical trials (22%), and observational studies (13%). Wysowski and Schwartz (2005) also discovered that spontaneous reports were the primary source of information used by the FDA for identifying postmarketing safety problems. The literature dealt with safety issues and not efficacy issues.

These findings in this body of literature might suggest that the role of postmarketing studies in safety labeling revision is limited. But, note that these studies looked at the design of the source of evidence only. They did not specify whether the source was a PMR/PMC. For example, some studies of analyses on spontaneous reports are established as PMR/PMCs (23 out of 1,405 FDAAA safety requirements were analyses of spontaneous reports during July 2008 – May 2016). Moreover, safety events from postmarketing studies may be reported to the FDA spontaneously (we don't know how many of them are from PMR/PMCs). The importance of spontaneous reports in label change doesn't necessary mean that PMR/PMCs are of little importance.

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<sup>114</sup> Whether there is a difference in the availability of data on the reasons for the label change depending on the initiators is unknown in this paper: Lester et al. used FDA's internal document database and determined who initiated the label change based on the supplemental applications and letters sent to sponsors by FDA. Those documents contain information on the basis of labeling revision.

#### **2.2.2.4 Value of PMR/PMCs**

CSDD (2007) assessed 61 PMCs from 20 companies for 34 products (29 for FDA) approved during 1998-2005. Unlike the other studies, CSDD sought to find out what drug firms thought about the value of the PM studies. It reported that “68% of clinical study sponsors and 79% of nonclinical study sponsors said their results contributed either marginally or not at all to their understanding of the safety, efficacy, or quality of their product. While the FDA testified to Congress that postmarketing studies have led to significant changes in how products are used, several industry observers say that the benefits resulting from increased postmarketing commitments, such as faster approvals and labeling changes, have yet to be verified.”

In addition, Pease et al. (2017) studied what other sources of information tell us about approved drugs after approval. They looked at 758 published studies (for 117 novel drugs for 123 indications initially approved between 2005 and 2012 on the basis of a single pivotal study and/or multiple pivotal studies with surrogate markers) and found that the post-approval clinical evidence varied substantially for novel drugs: across approval categories, in all features of trial design, except randomization, as well as in aggregated median numbers of studies and patient enrollment. They argue that the problem is not that post-approval studies are poorly designed or have negative efficacy results, but rather that they are not being published or performed at all. And, fewer than 10% of new drug indications had any published randomized, double blind trials that claim superior efficacy based on clinical outcomes that examined the same approved indication after 5.5 years of follow-up.

These study findings enlighten us on important issues, but their study samples lack the capacity to grasp the fuller picture of the use of PMR/PMCs by the FDA. The Booz Allen and CSDD studies did not examine requirements and postmarketing studies after the FDAAA of 2007

(these studies largely predate the currently available data). Fan et al. (2016) looked at only transporter-related PMR/PMCs and the CSDD study relies solely on survey responses from industry officials for evaluating the impact of PMR/PMCs on public health. Furthermore, the literature on the source of evidence for labeling revision focuses only on safety labels.

In conclusion, we have little evidence on how valuable PMR/PMCs are in terms of providing prescribing information that could be translated into the public health benefit. Our ability to quantify or monetize the “value” of postmarketing studies is limited and it is very hard. It is my hope that this paper adds more information on this challenging question by looking at the regulatory actions based on postmarketing studies.

## **2.3 Research questions, Methods, and Data**

### **2.3.1 Research questions**

The research question at hand is how likely a postmarketing study leads to regulatory actions and what factors affect the likelihood of label changes. By answering them, this study aims to evaluate the value of PMR/PMCs in terms of public health impact. Measuring public health impact of PMR/PMCs directly can be difficult, but a few proxy measures can be developed. One of them is information dissemination that could result in better prescribing decisions: better prescribing decisions can be translated into public health. A number of researchers have looked at the effect of warnings in drug labels and FDA’s safety communications on health behaviors and outcomes as well as knowledge, attitudes, and beliefs. Although the effects of FDA’s communication vary, physicians and patients generally became aware of and responded to black

box warnings and warnings (Gibbons et al., 2007<sup>115</sup>; Karpel et al., 2009). Dusetzina et al. (2012) found that recommending greater monitoring does not appear to have significant impact, but warning information appears to have been adopted more quickly under certain conditions.<sup>116</sup>

A drug's presence in the market can be changed by a firm's voluntary initiative or by FDA's order. Although (voluntary or involuntary) market withdrawal and restricted distribution are rarer than label changes (Wysowski and Swartz, 2005), those market status changes can have larger and more immediate public health impacts.

FDA may also require Risk Evaluation and Mitigation Strategies (REMS)<sup>117</sup> when new information about safety risks arises. Essentially, a REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such drugs by managing their safe use (FDA, 2009). So far, about 58% of drugs with REMS approvals also have PMR/PMCs. A few studies looked at the impact of REMS on public health in a small sample of drugs: Hollingsworth et al. (2015; 2016) showed that after REMS for erythropoiesis-stimulating agents, the use of the agents decreased significantly and Sarpatwari et al. (2015) claimed that the evidence indicates that off-label use of a drug declines when REMS was issued. It seems appropriate to consider REMS as a regulatory action FDA can take based on the results of PMR/PMCs.

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<sup>115</sup> Gibbons et al. found that SSRI prescriptions for children and adolescents decreased after warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with decreases in suicide rates in children and adolescents.

<sup>116</sup> When warnings are specific, reinforced with repeated, sustained messaging over time and when there are alternative treatment options available, medication warnings are more likely to be effective. (Dusetzina et al., 2012)

<sup>117</sup> The FDAAA of 2007 provided FDA with authority to require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)

Finally, in its implementation plan of FDAAA 2007<sup>118</sup>, the FDA notes that information that triggers changes in safety-related labels under section 505(o)(4) generally address the following sections of the label: boxed warnings, contraindications (section 4), warnings and precautions (section 5), adverse reactions (section 6), and drug interactions (section 7). Label changes<sup>119</sup> can be ranked by their potential influence on limiting drug use.<sup>120</sup> Three interviewees<sup>121</sup> confirmed that a boxed warning is the strongest, followed by contraindication, warnings and precautions, and adverse reactions. Efficacy labeling revisions pertain chiefly to indications and usage.

### 2.3.2 Data

In this study, the sample consists of New Drug Application (NDA)/Biologic License Application (BLA) approvals in 2008. The sample of drug-approvals in 2008 allows me to answer the research questions because the sample includes both postmarketing requirements and commitments after the FDAAA of 2007. And, it allows 9 or more years to observe fulfilled PMR/PMCs and FDA's follow-up actions including market status change and labeling revision.

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<sup>118</sup> Implementation of section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(4)), which was added by section 901 of the FDAAA: safety labeling revisions <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>

<sup>119</sup> Label changes include black boxed warning (BBW), indications and usage (label section 1), dosage and administration (label section 2), contraindications (label section 4), warnings and precautions (label section 5), adverse reactions (label section 6), drug interactions (label section 7), and use in specific population (label section 8). There are other sections—clinical pharmacology (label section 12), nonclinical toxicology (label section 13), clinical studies (label section 14), and patient counseling information—which are not considered as important as other changes in terms of influencing prescribing behaviors.

<sup>120</sup> Three interviewees (a lung disease specialist at UPMC in Pittsburgh, an infectious disease specialist at VA in Pittsburgh, and an allergist/immunologist in Maryland) confirmed that a boxed warning is the strongest, followed by, in order, contraindication, warnings and precautions, and adverse reactions.

<sup>121</sup> (1) lung disease specialist at UPMC in Pittsburgh, (2) infectious disease specialist at VA in Pittsburgh, and (3) allergist/immunologist in Maryland

Defining a “drug” can be tricky. A drug could be a drug product (with different forms and dosages), a brand name, or an active ingredient. A drug could have multiple NDA/BLA numbers and multiple drug products could share the same NDA/BLA number. And, a postmarketing study can be required for multiple NDA/BLAs. In this study, the meaningful units of analysis are “drug-approvals,” “approvals” and “postmarketing study.”

A drug-approval is a unique NDA/BLA number that is associated with a drug. An “approval” is a new or supplemental approval associated with a specific NDA/BLA number. A postmarketing study is a unique study that is associated with a specific approval. Postmarketing study ID<sup>122</sup> was created by combining NDA/BLA number, original or supplement, supplemental approval sequence number, study type (FDAAA safety study, confirmatory trial for accelerated approval, PREA pediatric study, and PMC), and study description.

In this sample, I included all new approvals (“B” and “N” codes<sup>123</sup>) and relevant supplemental approvals made in calendar year 2008. That means this sample includes some drugs originally approved before 2008 because supplemental approvals can be made at any time while the drug is in the market. Supplemental approvals included in the sample are new or modified indications, new dosage, new patient population, accelerated approval, and efficacy supplement with clinical data to support (“SE” codes in old data scheme) as well as unspecified supplemental approvals (general “S” codes). For “labeling revision” approvals and “manufacturing change” approvals in 2008, I found 1 out of 31 manufacturing changes and 3 out of 716 labeling revisions

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<sup>122</sup> FDA doesn’t provide study ID. PMS Set number can be used as part of ID, but PMS SET number isn’t publicly available. On phone conversations with FDA’s PMR/PMC data managers, they confirmed that ID can be made with these combinations. For example, Herceptin (BLA 103792), a cancer drug, had a supplemental approval (S5175) on January 18, 2008 with 4 PMCs. One of the PMCs was “To conduct a QT protocol according to the principles of ICH E14.....” This PMC’s ID is “103792S5175PMCTo conduct a QT protocol according to the principles of ICH E14.....” in my dataset.

<sup>123</sup> Code “B” is for BLA (Biologics License Application) and “N” is for NDA (drugs).

had postmarketing studies when linked up with PMR/PMC data. I excluded these cases. Also, I excluded formulation changes, package changes, and control supplements because they are rarely related to clinical safety and efficacy matters that are subjects of postmarketing studies.

By accessing FDA's quarterly updated PMR/PMCs and FDA approval datasets and through Freedom of Information Act requests, I created a list of PMR/PMCs associated with drugs approved in 2008. A single drug or a single approval might have multiple PMR/PMCs. For example, Cimzia (certolizumab pegol, a tumor necrosis factor TNF inhibitor, BLA 125160 original) was approved in April 2008 with one PREA study and five FDAAA safety studies. In May 2009, a supplemental application (BLA 125160-S80) was approved with one PREA study and one FDAAA study. Another FDAAA study was added to the original approval in November 2011.

I also acquired the current status of the PMR/PMCs as of January 2018 (then updated on April 2018). Table 2-4 describes the category of the status of postmarketing studies provided by FDA and the number of studies in each status in the sample. There are 13 studies (11 studies, excluding PREA studies) whose status is unknown because data is missing (4 PMCs were found on approval letter, but they were not included in the FDA PMR/PMC dataset) or disappeared in the PMR/PMC database (9 studies disappeared in the FDA quarterly datasets).

**Table 2-4. PMR/PMC status defined by FDA**

Status	Description
Fulfilled (122)	FDA has reviewed the PMR/PMC final report and notified the sponsor that the PMR/PMC has been satisfied
Submitted (0)	The sponsor has concluded or terminated the study and has submitted a final study report to the FDA, but FDA has not yet notified the applicant in writing that the study commitment has been fulfilled or released
Released (53)	FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study because the study is either no longer feasible or would no longer provide useful information.
Terminated (0)	The applicant ended the study before completion, and has not yet submitted a final study report to the FDA.



**Table 2 4. PMR/PMC status defined by FDA (continued)**

Status	Description
Ongoing (13)	The study is proceeding according to, or is ahead of, the original schedule. The FDA considers a study to be ongoing until a final study report is submitted to the FDA, as long as the activities are proceeding according to the original study schedule. If patient accrual or animal dosing has started but is not complete, and the projected date for completion of that milestone has passed, the study should be categorized as delayed.
Delayed (7)	The progression of the study is behind the original study schedule. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final study report to the FDA. While the original study schedule — not a revised schedule — serves as the basis for defining a study as delayed, each phase of the study will be considered in its own right. If the applicant has one delayed phase, but gets back on schedule during the next phase, the delayed status will no longer apply.
Pending (7)	The study has not been initiated (i.e., no subjects have been enrolled or animals dosed), but does not meet the criterion for delayed (i.e., the original projected date for initiation of patient accrual or initiation of animal dosing has not passed).

[source: FDA guidance on Postmarketing Requirements and Commitments: Status and Fulfillment Categories]<sup>124</sup>

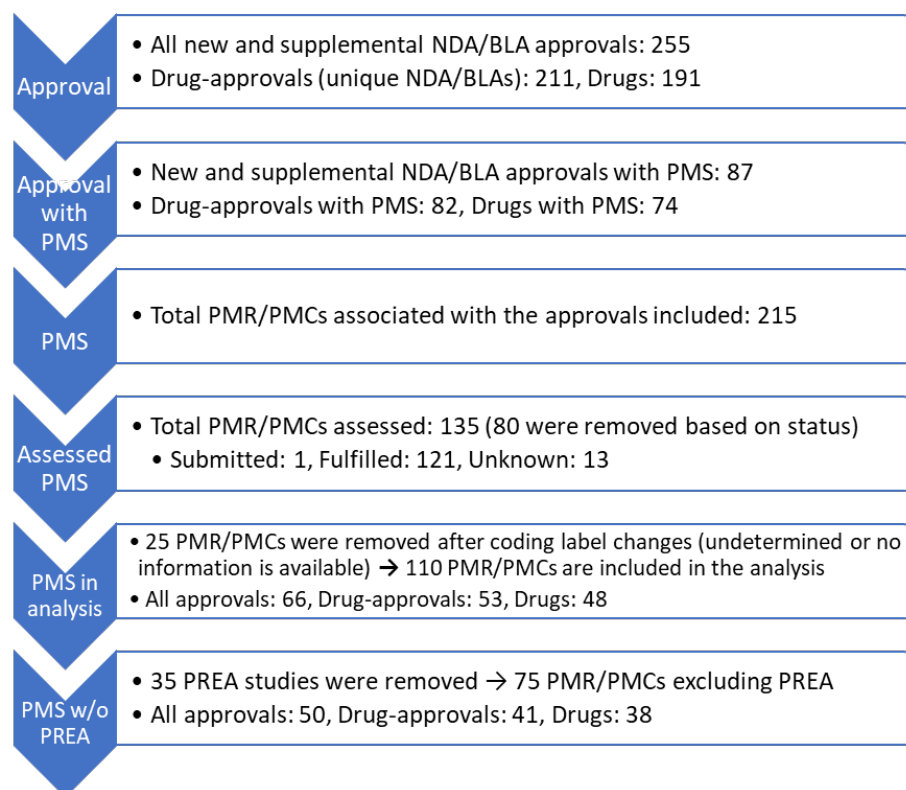
Notes:

1. The number in parentheses tells the number of each category of status in the sample, as of April 2018.
2. The status for 13 studies are unknown as of April 2018.

Figure 2-2 shows the process of study sample selection. A total of 255 new and supplemental approvals were selected based on approval type (new and various types of supplemental approvals)—this includes 211 unique drug-approvals. Among 255 approvals, 87 approvals (82 unique NDA/BLAs) had PMR/PMCs. A total of 215 PMR/PMCs were identified as PMR/PMCs associated with the 87 approvals in the sample. Out of 215 PMR/PMCs, 122 studies had been fulfilled and status for 13 studies were unknown, which made a sample of 135 accessible PMR/PMCs.<sup>125</sup> The studies with status “unknown” were included in the analysis because it is likely that these studies were closed. For example, the final reports for two of the “unknown” studies were submitted and another one had label change based on the postmarketing study.

<sup>124</sup> <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070799.htm>

<sup>125</sup> Eighty PMR/PMCs were removed because they are ongoing, delayed, pending, or released.



**Figure 2-2. Study sample selection process**

After coding the label changes and other regulatory actions for 135 studies, 24 PMR/PMCs were excluded from the analysis because I could not determine whether the label had been changed. The process for determining whether there were label changes is described in methods Section 2.3.3 and Appendix G. In one other case (NDA #22104), data were missing. That gives this analysis a total of 110 PMR/PMCs.

For modeling the probability of label changes, I excluded PREA pediatric studies (N=35) because they are fulfilled when labeling revision supplements are submitted.<sup>126</sup> PREA studies are more likely to have label changes compared with other PMR/PMCs and the inclusion of PREA studies would increase the probability of label changes.

Table 2-5 presents a snapshot of characteristics of approvals with or without PMR/PMCs in the 2008 sample. In this sample, 34% of NDA/BLA approvals were approved with PMR/PMCs. The percentage of approvals with PMR/PMCs differs greatly between new and supplemental NDA/BLAs (60% for new and 20% for supplemental). This contrast is not surprising because the safety profiles of older drugs are more finely defined than new drugs. The difference in the number of drug-approvals and approvals comes from multiple supplemental approvals per NDA/BLA.

**Table 2-5. Approvals in the 2008 sample**

	Approvals with PMR/PMCs	Approvals without PMR/PMCs	Total
All approvals	87 (34%)	168	255
New approvals	53 (60%)	35	88
NMEs	22 (92%)	2	24
Non-NMEs	31 (48%)	33	64
Supplemental approvals	34 (20%)	133	167
NDAs	75 (37%)	129	204
BLAs	12 (24%)	39	51
Expedited approvals	20 (39%)	31	51
AA	8 (100%)	-	8
Non-AA expedited	12 (28%)	31	43
Orphan drugs	10 (77%)	3	13
REMS	14 (50%)	14	28

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<sup>126</sup> Not all 35 PREA studies (fulfilled (33) / submitted (1) / unknown (1)) resulted in label changes. BLA #125057 had a PREA requirement and this requirement disappeared in the database after the 4<sup>th</sup> quarter of 2014. But, no label was changed concerning this specific PREA. Also, there are three PREA studies with BLA #125118—one of them was undetermined thus not included in the sample. The other two PREA requirements resulted in no label change because they only changed “minor” sections. One of the PREA requirements for NDA #211506 didn’t result in label change because the FDA and sponsor decided not to change the label after reviewing the study. For NDA #22090, a PREA requirement didn’t result in label change: although the letter says this PREA was fulfilled, there was no label change on pediatric patient group that this PREA was supposed to study. Further coding rules and justification, see Appendix.

Note: Total 255 approvals include new approvals as well as supplemental approvals for new or modified indications, new dosage, new patient population, accelerated approval, and efficacy supplement with clinical data to support (“SE” codes in old data scheme) as well as unspecified supplemental approvals (general “S” codes). NME = new molecular entity

In Table 2-5, out of all expedited approvals (priority review, fast track, and accelerated approvals), 39% are approved with PMR/PMCs. The percentage is somewhat higher than the average 34%, but no big difference was observed between expedited and traditional approvals in terms of establishment of PMR/PMCs. Most of expedited approvals without postmarketing studies were priority reviews only<sup>127</sup>. A higher percentage of orphan drugs and new molecular entities (NMEs) were approved with PMR/PMCs (orphan: 77%, NME: 92%).

### **2.3.3 Methods**

#### **2.3.3.1 Data formation**

In order to get a list of fulfilled/submitted/terminated PMR/PMCs and their drug-application information, I linked the drug-approval database, expedited approval drug datasets, a dataset that contains PMR/PMCs information, and the quarterly PMR/PMC database that contains status information. I traced all PMR/PMCs associated with the drug approvals in 2008 and coded relevant variables. Then I obtained drug information such as approval dates, the current market status (discontinued, prescription), chemical type, application type (NDA, BLA, supplement), review class (priority, standard, orphan), and expedited approval paths (accelerated, fast track, and breakthrough). I also looked up all approval letters to identify indications (drug-disease class), FDA office/division in which approval letter was issued, and all other missing information in the

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<sup>127</sup> Priority review is simple expedited process to shorten FDA’s review time once a full application was received (PDUFA deadline for priority is 6 months compared to 10 months for standard review).

dataset. To this dataset, several variables were added, including (1) total number of PMR/PMCs assigned to a drug; (2) the disease class to which the drug is assigned (classified by disease area according to the World Health Organization classification rules<sup>128</sup> and then re-classified by using 8 therapeutic areas from Downing et al. (2017)<sup>129</sup> study); and (3) REMS assignment (at the time of approval and post approval).

And, finally, label changes were coded in this dataset. I compared all labels updated after approvals that are associated with a PMR/PMC. I used fulfillment date and final report submission date information to identify possible label changes associated with a PMR/PMC. I looked at label changes near the fulfillment date or final report submission date, and then I expanded the search. Fulfillment date information from FDA PMR/PMC database and clinicaltrials.gov database but sometimes labels can be updated before fulfillment date. Also, not all fulfillment dates are identified in the dataset (only quarter-year information is available for some PMR/PMCs).

Next, I identified label changes based on the study description. Table 2-6 describes how label changes were judged and coded (more detailed work process and evidence for each code is provided in Appendix G). When an approval letter or other sources (MedWatch, Safety Labeling Change, FDA safety communications) confirm the change, I marked it as “changed.” When the

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<sup>128</sup> WHO ICD-10 codes

<sup>129</sup> Downing et al. (2017) used 8 therapeutic areas: autoimmune, musculoskeletal, and dermatology; cancer and hematology; cardiovascular disease, diabetes, and hyperlipidemia; genitourinary and renal; infectious disease; neurology; psychiatry; and other. Downing, N. S., Shah, N. D., Aminawung, J. A., Pease, A. M., Zeitoun, J. D., Krumholz, H. M., & Ross, J. S. (2017). Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *Jama*, 317(18), 1854-1863.

source of evidence is not available, but the PMR/PMC addresses a question that is specific enough to identify in the label, then I also marked it as “changed.”<sup>130</sup>

Among 67 PMR/PMCs that resulted in labeling revision, 72% (48 studies) had approval letters confirming the source of evidence for labeling revision. Excluding PREA studies, among 37 PMR/PMCs with label changes, 57% (21 studies) had approval letters verifying the source. Out of the other 16 cases, I identified 8 contacts (4 sponsor regulatory manager and 4 researchers who published their studies) for 7 studies to confirm the source of evidence. Two of them responded and they could not confirm the source of evidence because that is proprietary information.

Although there is lack of evidence to identify sources for the label changes for the remaining 16 cases, I attempted to reduce the possibility of measurement error. To reduce the possibility of random measurement error, I coded the label change variables two times. To reduce the possibility of systematic measurement error, I followed the coding rules. I coded the label change variable when the study description is specific in terms of purpose (i.e. antibody study, DDI study with specific drug, specific dose comparison), duration (i.e. 48 week analysis report, 7 years follow-up), and/or population (i.e. age group between 3 and 7, patients with moderate or worse chronic kidney disease--Stage 3 or greater/using NKF GFR definitions). The coding rules as well as the evidence for my judgments can be found in Appendix G.

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<sup>130</sup> For example, BLA 125160 (Cimzia) had a FDAAA requirement: “CDP870-033, an ongoing open-label trial to assess the long-term safety of CIMZIA in patients with Crohn's disease who have previously completed trials CDP870-031 or CDP870-032. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA-treated patients. Patient follow-up will be extended to seven years from the start of treatment.” In October 2015, Section 5 Immunogenicity was updated: “In two long-term (up to 7 years of exposure), open-label Crohn's disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma...” Although the letter doesn't confirm the source of evidence for this label change, the study mentioned in the label and specific information of antibody response fit the description of this FDAAA study.

I marked a PMR/PMC “no change” if (1) the FDA decided not to change the label and this decision was confirmed by a source (2) a label was changed only in sections 12-14; (2); or (3) the PMR/PMC asks for a specific information, but such specific information wasn’t changed in the label. In cases where the FDA asked firms to conduct a study and submit the report that contains broad information (not specific enough) or cases where the FDA asked firms to develop methods rather than conduct studies, I marked “undetermined.” There was one “unknown” case that does not have enough data to search and identify information on labels and PMR/PMCs.

**Table 2-6. Coding “label change” outcome rules and required evidence**

Outcomes	Description	Evidence
Change (21)	Label was updated based on a PMR/PMC	Approval letter or other sources (MedWatch, Safety Labeling Change, FDA Safety Communication) confirm the change OR the updated data is specific enough to judge that the change reflects the results of a PMR/PMC
No change (38)	A label change was made based on a PMR/PMC, but not a major change (label sections 12, 13, and 14)*	Approval letter/another source confirms a change OR the updated data is specific enough to call a change based on a PMR/PMC. But, the change is not considered a major change.
	Label was not changed after considering evidence from PMR/PMCs—a conscious choice not to change the label	Sponsor and the FDA do not seek to do any action further (e.g. a sponsor doesn't seek approval based on the result of a PMR/PMC or FDA decides that the PMR/PMC doesn't support a change reasonably)
	PMR/PMC findings not relevant	No information/data was updated concerning a particular PMR/PMC that aims to answer a specific question AND there's no evidence that “no action” was a result of PMR/PMC review
Undetermined (15)	Can't determine whether the identified change was due to a specific PMR/PMC because study description is not specific enough AND/OR the changed data is not specific	Approval letter doesn't mention changes AND either or both of the following cases: (1) Changed information/data in a label is not specific enough to say that this change was from a PMR/PMC (2) A PMR/PMC is too general to find information/data that could have been changed in the label

**Table 2 6. Coding “label change” outcome rules and required evidence (continued)**

Outcomes	Description	Evidence
Unknown (1)	PMR/PMC status is unknown (missing data or disappeared). Whether the study was fulfilled or submitted is not clear.	No information on PMR/PMC and labels is available.

Note: \* these are mostly toxicology studies and enzyme studies. For label changes in sections 12, 13, 14 were coded as no change.

In order to see the impact of data quality of PMR/PMCs on revising labels, I coded the data quality based on study design. First, I classified studies as clinical trials, observational studies, and nonclinical studies. Clinical trials are classified as randomized and non-randomized trials based on the study descriptions and classification provided by the database on [clinicaltrials.gov](http://clinicaltrials.gov). For 11 out of 69 clinical trials among FDAAA requirements, accelerated approval requirements, and PMCs, I was not able to locate specific information on randomization and I classified them as non-randomized trials. Nonclinical studies include in vitro studies, animal toxicology studies, extrapolated PREA studies as well as genotypic and phenotypic analyses.

A variable “Total\_Exp” is created to capture the effect of expedited approval that might have unknowns to a greater degree. The variable is a count variable—the count of expedited approval paths (priority review, accelerated approval, and fast track designations) designated to a drug approval. Thus, it ranges from 0 to 3. Varying the degree of expedited process allows better prediction of label changes. REMS requirement associated with approvals tells us the perceived level of risk of a drug.

Lastly, I coded the study purpose with 4 categories: (1) safety studies; (2) efficacy studies; (3) dose finding studies; and (4) other. All FDAAA studies belong to safety studies and all accelerated approval confirmatory studies belong to efficacy studies. Safety studies include long-term safety studies, drug-drug interaction studies, specific risk factor studies such as QT interval,



toxicology studies, safety of specific doses, breast milk – infant exposure studies, etc. Efficacy studies are mainly confirmatory trials for accelerated approvals and PREA studies, but they include efficacy commitment studies on specific population and on specific dosage. For studies whose goals are both safety and efficacy findings in the study descriptions, I looked them up in [clinicaltrials.gov](http://clinicaltrials.gov) and coded the primary outcome measure as safety or efficacy.<sup>131</sup> Dose findings are related to both safety and efficacy, and thus classified as a separate category. Other studies include enzyme/protein/amino acid studies, bioavailability studies, PK studies on specific population under certain conditions, and susceptibility studies. Using this classification, I coded safety as 1 if the PMR/PMC belongs to safety studies. Otherwise, I coded safety as 0.

### **2.3.3.2 Conceptual framework**

PMR/PMCs are carried out to reduce important uncertainties surrounding safety and efficacy that remain at the time of drug approval. If there was a greater confidence on a drug's safety and efficacy issues at the time of approval, it is less likely that postmarketing studies will require labeling revision after the drug is marketed. The initiation of postmarketing studies should therefore be related to the likelihood that new information will be discovered that could lead to label changes. It is because postmarketing studies are a marker for uncertainty and the studies themselves provide additional information.

But, PMR/PMCs are not the only source of new information that leads to labeling revision. Although postmarketing studies provide one source of new information, other sources—e.g., spontaneous reports not being part of PMR/PMCs—are also likely to lead to labeling revisions when initial uncertainty is higher.

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<sup>131</sup> In all three cases, the primary outcome was efficacy: progression free survival

When a PMR or PMC is established, we can think about two possible paths: (1) the study is carried out and completed (fulfilled) or (2) the study is not carried out or not completed (all other status than fulfilled). When the study is not carried out or not completed, we do not expect that the label is changed due to the information from the study.

But, when a study is fulfilled, we can think of several possible outcomes depending on the result of the study:

- a) The result may be indeterminate
- b) The result may confirm prior assumptions and not lead to label changes
- c) The result support some label changes:
  - i. No label changes are made because the postmarketing study was not the sufficient cause.
  - ii. The label was changed, but other source triggered the change (e.g., spontaneous reports)
  - iii. The label change has several causes and the postmarketing study is one of them, but no single source would have been sufficient.
  - iv. The label is changed due to the information from the postmarketing study.

In case of (a), the result of a study is indeterminate therefore no action can be initiated due to the study. In case of (b), the result confirms the prior belief and thus no action is required. In case of (c), result of a postmarketing study can support label change. However, the study result may or may not lead to label change: (i) no label is changed because the postmarketing study alone is not the sufficient cause of label change (in this case, no other information is available or other source of evidence doesn't support label change); (ii) the label was changed due to other source of

evidence (other source of information is more credible or convincing in this case); (iii) the study is one of the sources of information that led to label changes and no single source would have been sufficient; or (iv) the label is changed due to new information from the study (even when other source of information is available, the study result is more pivotal for the label change).

These distinctions are useful for the question of causation. Although (c)(iii) is not a complete causal mechanism for label change, (c)(iii) and (c)(iv) both make case for causality. If we find that drugs with postmarketing studies are more likely to have label changes than drugs without postmarketing studies, then it may support (c)(iii) or (c)(iv). It is unlikely that the positive association between the existence of postmarketing studies and label changes would be observed if postmarketing studies didn't cause label changes in the case of (c)(i) or (c)(ii).

Furthermore, among the drugs with labeling revision made in a certain period of time, the percentage of drugs with postmarketing studies is expected to be higher than the percentage of drugs without postmarketing studies, if postmarketing studies caused labeling revision. And, we can also test whether such associations are observed differently in safety and efficacy labeling.

To examine the relationship further, we can compare drugs with fulfilled postmarketing studies only and drugs with unfulfilled postmarketing studies only in terms of label change. A potential bias from drug characteristics that may influence the label changes in the postmarketing setting could be reduced to some extent by using the sample of drugs with postmarketing studies. If we observe drugs with fulfilled postmarketing studies only are more likely to have label changes than drugs with unfulfilled postmarketing studies only (where none of postmarketing studies was fulfilled), it supports (c)(iii) and (c)(iv).

Now, let us turn to the question of when postmarketing studies result in label changes. We can examine a sample of drug approvals with postmarketing studies to see how much of label

changes was based on the findings of the studies and how likely a postmarketing study would result in labeling revision under certain conditions. As explained in data section above, for each postmarketing study, I coded label changes due to the study. The following conditions (variables) are identified as factors that may affect the likelihood of label change.

***NME.*** We hypothesize that FDA is more attentive to information for drugs with “unknowns” such as NMEs. Booz Allen noted that FDA “reviewers take into account the potential benefit of a drug when determining whether an issue can be resolved post-approval” and that novel drugs “are likely to have more unknowns, which would also explain the greater number of issues to resolve in the postmarketing phase.”

***Expedited approval.*** This also suggests that FDA is likely to pay more attention to the drugs with expedited approval paths in the postmarketing setting. Confirmatory trials are mandated for accelerated approvals, and thus full approval should be based on the findings from the AA requirements. But, drug with other expedited approval paths are also likely to have more safety label changes (Mostaghim et al., 2017). Therefore, we expect that drugs with expedited approval are more likely to have label changes.

**REMS.** REMS<sup>132</sup> is another avenue we can explore. FDA requires REMS for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. FDAAA requires FDA to consider the following six factors in making a decision about whether to require a REMS<sup>133</sup>: (1) seriousness of any known or potential adverse events; (2) expected benefit; (3) seriousness of the disease or condition; (4) NME; (5) duration of treatment; and (6) size of the population. Since REMS is designed to manage both known and unknown risks, drugs with REMS are “riskier” or “have more uncertain risk” compared to non-REMS drugs.

In the same vein as NMEs, we expect that drugs with REMS are more likely to have label updates than drugs without REMS, holding others constant. FDA may be more vigilant about the drugs with “risks” or “more uncertain risk” and actively use postmarketing information from PMR/PMCs about those drugs to inform the public. Some might argue that drugs with REMS are more likely to have postmarketing studies and thus label changes may be made due to the studies<sup>134</sup>. However, the percentage of drugs that had label changes is higher in drugs with REMS (79%) compared to drugs without REMS (46%).<sup>135</sup> Even when controlling for the existence of

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<sup>132</sup> “A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks. A REMS may consist of a Medication Guide, a patient package insert, and/or a communication plan. FDA may also require certain elements to assure safe use (ETASU) as part of a REMS. The ETASU can include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions....REMS generally must have a timetable for submission of assessments of the strategy.” In FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary: Guidance for Industry, FDA (September 2016)

<sup>133</sup> RiskMAP, a predecessor to REMS, was designed to minimize the known risks of drugs and much of the principles described in the RiskMAP guidance are reflected in the REMS provisions (FDA guidance on REMS, 2016)

<sup>134</sup> Out of 255 approvals in 2008, 28 approvals had REMS and 227 approvals didn’t have REMS. Out of 28 approvals with REMS, 50% had PMS while 32% had PMS for 227 approvals without REMS.

<sup>135</sup> Among 173 drugs that had approvals in 2008 with information on label change (I excluded 29 drugs that had REMS after 2008), 24 had REMS and 149 had no REMS. Among 24 drugs with REMS, 19 drugs had label changes (79%). Among 149 drugs without REMS, 69 drugs had label changes (46%).

postmarketing studies, we observe that drugs with REMS are more likely to have labeling revision than drugs without REMS.<sup>136</sup>

***The number of PMR/PMCs.*** The number of PMR/PMCs associated with a drug might be proxy for “unknowns” at the time of approval. Thus, the number of PMR/PMCs is more likely to be positively associated with labeling revisions.

***Requirement vs. Commitment.*** The distinction between requirements and commitments may be a factor that is associated with labeling revision. PMCs are agreed studies without legal binding force while PMRs are mandatory or required by FDA. Confirmatory trials for accelerated approvals are mandatory and thus label change (full approval) is expected to result from the AA studies. PREA studies are also requirements with aim to claim new indications on pediatric patients.

The 2007 FDAAA created safety requirements, and thus divides safety studies into requirements and commitments. Although FDA doesn’t specify when it requests safety studies rather than requires it, we may assume that PMRs deal with more critical issues because FDAAA safety studies are required when there is a need to address “serious risk” (a known serious risk, signals of serious risk, or an unexpected but potential serious risk). According to the BAH study, “PMCs...do not represent major unaddressed safety and efficacy concerns, but instead are intended to further refine the safety, efficacy, or optimal use of a product, or to ensure consistency and reliability of product quality.” Therefore, if PMRs are dealing with more important safety

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<sup>136</sup> Within the drugs with postmarketing studies, drugs with REMS are more likely to have labeling revision than drugs without REMS (86% vs. 63%). Within the drugs without postmarketing studies, drugs with REMS are more likely to have labeling revision than drugs without REMS (70% vs. 37%).

concerns, requirements will be more likely to lead to label changes compared to commitments, when controlling for other drug characteristics and study design.<sup>137</sup>

**Study design.** Finally, study design (type of data source) matters in terms of “evidentiary” weight. In many cases and in theory, randomized controlled trials (RCT) provide the highest quality evidence that a drug is effective. Although in a practical sense, observational studies may provide good quality and sufficient evidence regarding a drug’s safety, trials usually do a better job of isolating the impact of the drug. In-vitro studies and nonclinical studies are more likely to be updated in 12-14 label sections that are considered minor changes.

## 2.4 Results

### 2.4.1 Label changes and PMR/PMCs

Were drugs with PMR/PMCs more likely to have label changes than drugs without PMR/PMCs? To answer the question, first, we will look at new drug approvals (NDA/BLAs) approved in 2008.<sup>138</sup> Among 85 drug approvals identified, 2 drugs were excluded from the analysis because they had two original approvals and earlier original approvals were granted before 2008. This makes a sample of 83 new drug approvals.

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<sup>137</sup> Sixty percent of safety PMRs had labeling revision (28 out of 47) while 47% of safety PMCs (8 of 17) had labeling revision.

<sup>138</sup> I did look at 2009 and 2010 approvals to expand the sample of drug approvals. Find Table 2-25 in Appendix D.

As shown in Table 2-7, 84% of all drug approvals (70 out of 83) had label changes at some point until June 1, 2018 when including all label changes (this includes any kinds of labeling revisions such as simple wording changes, data updates in label sections 12-14, etc.) And, 68% of all drug approvals (56 out of 83) had PMR/PMCs. Among 70 drug approvals with label changes, 17 had label changes without PMR/PMCs (24%).

**Table 2-7. Label changes, comparing drugs with PMR/PMCs to drugs without PMR/PMCs**

	With PMR/PMCs	Without PMR/PMCs	Total
Label changed	53 (95%)	17 (63%)	70
No label changed	3 (5%)	10 (37%)	13
Total	56	27	83

Notes:

1. The sample includes all new drugs approved in 2008. Labeling revision supplemental approvals (including efficacy and other supplemental approvals, excluding Chemistry, Manufacturing, and Controls and REMS revisions) after original approval until June 1, 2018 were identified.
2. The dataset was linked to PMR/PMC data.
3. The sample excludes 18 drug approvals: 16 drug approvals that have no further information on label changes or PMR/PMCs, and 2 drugs that had two original approvals (the earlier original approval was granted before 2008)

Table 2-7 also shows that drugs with PMR/PMCs were more likely to have labeling revisions. Out of 56 drugs with PMR/PMCs, 95% (53) of them had labeling revisions compared to 63% (17 out of 27) of drugs without PMR/PMCs ( $p < 0.001$ ). But, again, this includes label updates that are less relevant to prescribing drugs for patients.<sup>139</sup>

Now, we want to look at more meaningful labeling revisions that contain prescribing-relevant information—black box warnings for safety labeling and indications for efficacy labeling. How many drugs with PMR/PMCs had label changes on black box warning (BBW) and indications and how many drugs without PMR/PMCs had such changes?

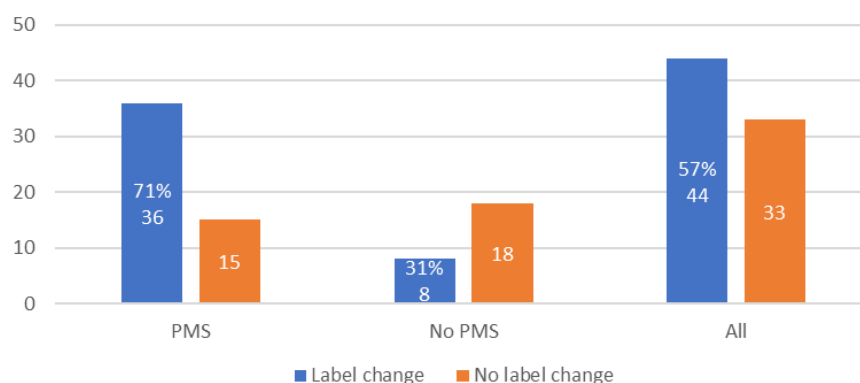
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<sup>139</sup> Some parts of drug label are less relevant for making prescribing decisions. For example, label sections 11, 12, 13, 14, and 16 are less likely to provide information when making prescribing decisions (11. Description and 12. Clinical pharmacology 13. Nonclinical toxicology 14. Clinical studies and 16. How supplied/storage and handling).



In order to answer this question, we need a sample of drug-approvals with PMR/PMCs on 2008 or later and drug approvals without PMR/PMCs. Out of 83 new drug approvals (NDA/BLAs) from Table 2-7 above, I excluded 6 drug approvals whose labels and approval letters<sup>140</sup> are not available. This gives a total of 77 drug approvals—51 drugs with PMR/PMCs on 2008 or later and 26 drugs without PMR/PMCs. (Table 2-21 in Appendix D) I coded each drug's label changes on BBW and indications.

Figure 2-3 shows that 71% of the drugs with PMR/PMCs had BBW or indication changes while only 31% of the drugs without PMR/PMCs had such changes ( $p < 0.01$ ). This difference (71% vs. 31%) is even larger than the difference of the percentage of any kinds of label changes with or without PMR/PMCs (95% vs. 63%) in Table 2-7 above.



**Figure 2-3. Drugs with label changes on BBW and indication, by the existence of PMR/PMCs**

Notes:

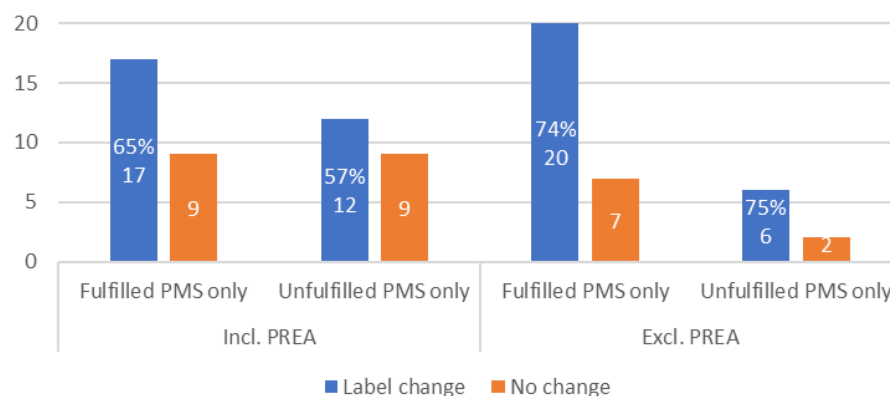
1. The sample includes drug-approvals (NDA/BLAs) that were granted in 2008. The sample includes changes on BBW and/or indications between 2009 and June 1, 2018. Either or both of the two changes is counted as a change.
2. The numbers inside the bars indicate the number of drug-approvals. The percentage inside the blue bars (for those drugs with label changes) indicate the percentage of drugs with changes on BBW and/or indications among all drugs with PMR/PMCs or without PMR/PMCs. For example, the first blue bar shows that  $71\% = 36 / (36 + 15)$  and this means that 71% of drugs with PMR/PMCs had label changes.
3. See Tables 2-21 and 2-22 in Appendix D.

<sup>140</sup> The labels and approval letters are required to see whether BBW and indication information was updated for a drug.

In order to see whether this positive association between PMR/PMCs and labeling revision is different in safety and efficacy labeling changes, Table 2-22 in Appendix D was created. The table shows that the association between PMR/PMCs and labeling revision was larger in efficacy labeling changes in indications than in safety labeling revisions on black box warnings.

To reduce some potential confounding factors, let us look at drugs with PMR/PMCs only. Among all drugs that had approvals and postmarketing studies in 2008, 26 drugs have fulfilled PMR/PMCs only and 24 drugs have unfulfilled PMR/PMCs only (among 24 drugs, 3 drugs had no information on indications) as of April 2018. Without PREA studies, 34 drugs have fulfilled PMR/PMCs only and 25 drugs have unfulfilled PMR/PMCs only (among 25 drugs, 3 drugs had no information on indications) as of April 2018.

Figure 2-4 shows that drugs had fulfilled postmarketing studies had more label changes on BBW and indications compared to drugs with unfulfilled postmarketing studies. Among all 26 drugs with fulfilled postmarketing studies, 17 had changes on BBW and/or indications (65%). Among 21 drugs with unfulfilled studies only, 12 had label changes (57%). When excluding PREA, the difference in the rates of label changes between drugs with fulfilled studies only and drugs with unfulfilled studies only becomes unnoticeable. It is 74% for drugs with fulfilled studies only and 75% for drugs with unfulfilled studies only. Among the drugs with important label changes, 59% of them had fulfilled PMR/PMCs and 41% had unfulfilled studies only. Note that the percentage of drugs with fulfilled studies only is 55% (26 out of 47). Without PREA, the difference disappears: 77% had fulfilled studies only and 35% had unfulfilled studies only, but the percentage of drugs with fulfilled studies without PREA was high (77%).



**Figure 2-4. Drugs with label changes, by fulfilled PMR/PMCs vs. unfulfilled PMR/PMCs**

**Notes:**

1. The sample includes drug-approvals that were granted in 2008. The sample includes changes on BBW and/or indications between 2009 and June 1, 2018. Either or both of the two changes is counted as a change.
2. The numbers inside the bars indicate the number of drugs. The percentage inside the blue bars (for those drugs with label changes) indicate the percentage of drugs with changes on BBW and/or indications among all drugs with fulfilled or unfulfilled PMR/PMCs. For example, the first blue bar shows that 65% = 17 / (17+9) and this means that 65% of drugs with only fulfilled PMR/PMCs had label changes.
3. In the sample, there are 26 drugs that have only fulfilled PMR/PMCs and 24 drugs that have only unfulfilled PMR/PMCs. When excluding PREA studies, 34 drugs have only fulfilled PMR/PMCs and 22 drugs have only unfulfilled PMR/PMCs.
4. In the sample, there are a total of 24 drugs with only unfulfilled PMR/PMCs. Out of those 24 drugs, 3 drugs had no information on indication. Thus, for label changes on black boxed warnings, the total number of drugs with unfulfilled PMR/PMCs is 24; the total number of drugs with unfulfilled PMR/PMCs for changes on indications is 21. Same for the sample excluding PREA studies.
5. For further data, see Tables A12 and A13 in Appendix

Table 2-8 separates safety and efficacy labeling revisions. The table tells us that fulfilled PMR/PMCs are not associated with BBW, but with indications. It shows that 12% of all drugs with fulfilled studies had BBW changes (3 out of 26) while 25% of drugs with unfulfilled studies had BBW changes (6 out of 24). But, for indication changes, 62% of drugs with fulfilled studies had label changes (16 out of 26) while 52% of drugs with unfulfilled studies had indication changes (11 out of 21).

**Table 2-8. Drugs with label changes, by fulfilled PMR/PMCs vs. unfulfilled PMR/PMCs, by BBW vs.**

Indication							
PREA	Fulfilled vs. Unfulfilled	BBW change			Indication change		
		Yes	No	total	Yes	No	total
All	Fulfilled studies only	3 (12%)	23	26	16 (62%)	10	26
	Unfulfilled studies only	6 (25%)	18	24	11 (52%)	10	21
w/o PREA	Fulfilled studies only	6 (22%)	21	27	18 (67%)	9	27
	Unfulfilled studies only	4 (36%)	7	11	5 (63%)	3	8

Notes:

1. For drugs with unfulfilled postmarketing studies, 3 of 24 had no information on indication. Thus, for changes on black boxed warnings, the total number of drugs with unfulfilled postmarketing studies is 24; the total number of drugs with unfulfilled postmarketing studies for changes on indications is 21. Same for the sample excluding PREA studies.
2. For the percentage of drugs with postmarketing studies and drugs without studies among the drugs that had BBW and other important label changes, see Appendix H.

Among drugs with changes on BBW, 33% (3 out of 9) had fulfilled PMR/PMCs while 67% (6 out of 9) had unfulfilled PMR/PMCs. Considering the fact that the percentage of drugs with fulfilled studies is 52%-55% (52% for BBW and 55% for indications due to 3 drugs with unavailable information), it seems that there is no role of postmarketing studies on BBW changes. But, among drugs with changes on indications, 60% (16 out of 27) had fulfilled studies and 40% (11 out of 27) had unfulfilled studies.

In Table 2-8, when excluding PREA studies, 50% of drugs with BBW changes had fulfilled PMR/PMCs only (6 out of 12) and 65% of drugs with indication changes had fulfilled PMR/PMCs only (22 out of 34). In Figure 2-4, we observed that the difference in the percentage of label change between drugs with fulfilled PMR/PMCs and drugs with unfulfilled PMR/PMCs was larger when PREA studies were included. Table 2-8 suggests that such difference is more apparent in safety labeling revisions rather than indication revisions.

In sum, drugs with PMR/PMCs are more likely to have label changes, especially important label changes. But, the association between PMR/PMCs and label changes seems different in

efficacy and safety labeling revisions. The association is weak in black box warnings while it is stronger in efficacy labeling changes.

#### **2.4.2 Regulatory actions: Withdrawal/discontinuation, REMS assignment**

FDA periodically notifies the list of drugs discontinued under the process in § 314.150(c) (21 CFR 314.150(c)).<sup>141</sup> The listed drugs were discontinued and withdrawn at the request of sponsors not based on efficacy or safety reasons. Out of 82 drugs that had approvals and postmarketing studies in 2008, 11 drugs were identified as discontinued/withdrawn after 2008. It was found that one of the 11 drugs was discontinued due to the lack of efficacy (Oforta, fludarabine phosphate, NDA #22273). It was approved in December 2008 with one PMR—accelerated approval confirmatory trial. FDA stated that the required postmarketing study had not been completed and clinical benefit had not been verified (federal register reference).

One drug, still in the market, had a withdrawal of indication. Avastin (BLA 125085) was approved for treatment of HER2-negative metastatic breast cancer with accelerated approval in February 2008. Although Genentech submitted the results of two clinical trials to satisfy the confirmatory trial requirement, FDA determined that these trials failed to verify AVASTIN's clinical benefit.

For risk evaluation and mitigation strategies (REMS), 19 PMR/PMCs with 8 drugs were associated with post-approval REMS—the sponsors of the 8 drugs had been required to implement

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<sup>141</sup> (c) FDA will withdraw approval of an application or abbreviated application if the applicant requests its withdrawal because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section applies to the drug. FDA will consider a written request for a withdrawal under this paragraph to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application or abbreviated application under this paragraph is without prejudice to refiling.

post-approval REMS. But, those REMS requirements were decided before the postmarketing studies associated with the drug approvals were fulfilled. In these cases, requiring REMS cannot be regarded as a result of the PMR/PMCs.

In conclusion, PMR/PMCs had some impact on changing market status: one of 11 drug discontinuations (9%) was based on PMR/PMCs and one indication was withdrawn based on PMR/PMCs. Both were accelerated approvals. None of REMS required after approval was due to the results of PMR/PMCs. However, even when no market status changes took place, as FDA staff noted in the BAH study, confirming safety and efficacy as well as satisfying or verifying concerns has public health benefit. No market status change may imply that the impact on validating concerns for market status was small, but the impact on confirming market status was large.

### **2.4.3 Logit and Ordinal Logit models on Label Changes**

Logit models for the binary outcomes and ordinal logit models for the ordinal outcome were tested. Logit models estimate the probabilities of label change, and here, the dependent variable (label\_change) is binary: whether or not a label was changed. Table 2-9 below describes statistics of the sample.

**Table 2-9. Descriptive Statistics**

Variable	Description	N	Min	Max	Mean	Std.D
Label_change	1: Label was changed 0: Label was not changed	110 (75)	0	1	0.609 (0.493)	0.490 (0.503)
Impact	0: No label change 1: “low” impact category –adverse reactions, drug interactions, and subpopulation 2: “high” impact category – BBW and indication, dosage, contraindication, warnings and precautions	110 (75)	0	2	1.082 (0.84)	0.930 (0.915)
Impact2	0: No label change 1: “low” impact category – dosage, contraindication, warnings and precautions, adverse reactions, drug interactions, and subpopulation 2: “high” impact category – BBW and indication	110 (75)	0	2	0.873 (0.6)	0.803 (0.678)
Total_PMS	The total number of PMRs and PMCs associated with the drug approval	110 (75)	1	9	4.073 (4.92)	2.179 (2.179)
Required	1: PMR 0: PMC	110 (75)	0	1	0.645 (0.48)	0.481 (0.503)
Design3	1: Randomized controlled trial 2: Non-randomized or unspecified trial 3: Observational study 4: Nonclinical study	110 (75)	1	3	1.682 (1.827)	0.928 (0.978)
Disease2	1: autoimmune, musculoskeletal, & dermatology 2: cancer and hematology 3: cardiovascular and diabetes 4: genitourinary and renal 5: infectious disease 6: neurology 7: psychiatry 8: other	110 (75)	1	8	4.682 (4.453)	2.501 (2.522)
Safety	1: safety study (primary purpose) 0: non-safety study	110 (75)	0	1	(0.653)	(0.479)
NDA_BLA	1: NDA, 0: BLA	110 (75)	0	1	0.836 (0.8)	0.372 (0.403)
REMS	1: the drug approval had REMS 0: no REMS	110 (75)	0	1	0.291 (0.32)	0.456 (0.470)
Total_exp	Total number of expedited designation assigned to a drug	110 (75)	0	3	0.445 (0.56)	0.819 (0.889)

Note: The numbers in parentheses are statistics excluding PREA studies.

Ordinal Logit models estimate the probabilities of impact of label change; the dependent variable is categorical: impact category of label changes. The variable “impact” is 2 (“high” impact category) if the PMR/PMC changed the sections of BBW, indication, dosing, contraindication,

and warnings. “Impact” is 1 (“low” impact category) if the PMR/PMC contributed to label changes in the sections of adverse reactions, drug interactions, and subpopulation). “Impact” is 0 (“no” impact category) if no label change was made.

The variable “impact2” uses slightly different classification of impact level. When there was a change in BBW and/or indications that has the highest potential impact, it is 2. For other label changes (dosing, contraindications, warnings, adverse reactions, drug interactions, and subpopulation), “impact2” is coded as 1. For no label changes, it is zero. Note that there was no BBW identified as a result of PMR/PMCs and this makes the variable “impact2” as indicator of whether there was change in indications.<sup>142</sup>

#### **2.4.3.1 Final models**

Table 2-10 presents chosen models for logit and ordinal logit analyses. The estimated probability of label change is 54% (Delta-method standard error: 0.1207,  $p < .001$ ): the percentage of label change in the sample is 49%. We find positive effects of the total number of PMR/PMCs, requirement, quality of data (study design), cardiovascular and diabetes drugs, psychiatric drugs, biologics, and expedited approval on the likelihood of label change and impact level.

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<sup>142</sup> Twelve drugs had black box warnings after 2008 approval (26 fulfilled PMR/PMCs were associated with those 9 drugs). Among 12 drugs, 9 drugs had BBWs that are not associated with any fulfilled PMR/PMCs. For 3 drugs, it was undetermined whether or not PMR/PMCs led to BBW revisions. More detailed justification is provided in section 3 in Appendix G.



**Table 2-10. Logit and OLogit Regression Results**

<i>Odds (t stat)</i>	Logit (m1) Label_change	Ologit (m2) Impact	Ologit (m3) Impact2
Total_PMS Required Design	1.31 (0.9) 110.5** (2.78)	1.099 (0.48) 8.538* (2.32)	1.097 (0.46) 66.80** (3.28)
2	0.0632* (-2.02)	0.0996* (-2.45)	0.152* (-1.99)
3	0.000883* (-2.22)	0.0127* (-2.19)	0.00433* (-2.57)
4	0.0553* (-2.31)	0.0758** (-3.07)	0.102* (-2.56)
Disease			
2	0.483 (-0.53)	0.58 (-0.47)	0.586 (-0.45)
3	535.3* (2.49)	18.13 (1.8)	59.24* (2.36)
5	3.019 (0.74)	0.8 (-0.17)	1.636 (0.36)
6	0.591 (-0.29)	3.221 (0.87)	0.533 (-0.45)
7	150.3* (2.12)	61.97** (2.68)	107.5** (2.79)
8	2.155 (0.5)	0.944 (-0.05)	1.708 (0.41)
NDA_BLA	0.001* (-2.20)	0.006*** (-3.51)	0.007** (-3.18)
Total_Exp	2.559 (1.12)	1.907 (1.15)	3.919* (2.3)
REMS	0.0461 (-1.81)	0.0513* (-2.31)	0.107 (-1.72)
Safety	0.119 (-1.35)	0.512 (-0.80)	0.0839* (-2.19)
BIC	115.584	156.250	149.563
AIC	78.504	116.853	110.166
Observations	75	75	75
LR chi2	57.45	64.29	66.43
Prob > chi2	0.0000	0.0000	0.0000
Pseudo R2	0.5527	0.4369	0.4658
Log likelihood	-23.252149	-41.426475	-38.082977

Notes:

1. \*: p<0.05, \*\*: p<0.01, \*\*\*: p<0.001
2. Odds ratio. Exponentiated coefficients (t-stat in parentheses)
3. The unit of analysis is postmarketing study. N=75 studies without PREA studies
4. The number of drug-approvals is 41

Although statistically insignificant, we also observe that the total number of expedited approval designations is positively associated with the probability of label changes.

On the other hand, we observe that REMS requirement and safety study are negatively associated with the probability of label change and impact level. These are not statistically significant in the logit model, but somewhat significant in the ordered logistic model.

Model tests were performed. Likelihood-ratio test and Wald test results for both models show statistical significance. The Brant test was performed for the ordered logit models to find if underlying parallel assumption was violated. The parallel assumption underlying ordered logistic

regression is that the relationship between each pair of the outcome groups is the same. The Brant tests with ordinal models did not show statistical significance. It tells us that the models with the specified independent variables didn't violate the parallel assumption. See Table 2-17 in Appendix D for the assumption test results for both models.

#### **2.4.3.2 Required and Study design (data quality)**

As we hypothesized in Section 2.3.3, the probability of label change and the impact level (based on the importance of label sections to prescribing drugs) increases when a postmarketing study is required and study design quality (data quality) increases (statistically significant  $p < .05$ ).

Among 75 PMR/PMCs without PREA studies, 79% of randomized controlled trials had label changes while only 20% of nonclinical studies had label changes (see Appendix E for further description). Although these variables are statistically significant, the odds ratios of label changes are very different. The odds of having more impactful labeling revision are 194% more for required studies ( $z=2.319$ ,  $p < .05$ ) in model 2 (high impact group includes sections 1-5 of drug labels) and 727% more for required studies ( $z=3.276$ ,  $p < .01$ ).

Since AA studies are aimed for full approval and PREA studies are required for pediatric indications, we can compare PMR safety studies with PMC safety studies: 60% of safety PMRs had labeling revision (28 out of 47) while 47% of safety PMCs (8 of 17) had labeling revision. Even without AA and PREA studies, safety PMRs are more likely to have labeling revision than safety PMCs.

Whether or not a study was required dominates the change in predicted probabilities of labeling revision rather than data quality. Table 2-11 below presents the predicted probabilities of label change by "requirement" and data quality. The effect of "requirement" is larger in non-randomized trials (80% difference in predicted probability, 0.851-0.049) and nonclinical studies

(79% difference, 0.833-0.043). The effect is smaller in RCT (54% difference, 0.989-0.449), which implies that randomization matters.

**Table 2-11. Predicted probabilities, by requirement and design**

	Required	Non-required	Difference
RCT	0.989	0.449	0.54
Non-R CT*	0.851	0.049	0.802
Observational	0.074	0.001	0.073
Nonclinical	0.833	0.043	0.790

Notes:

1. Other covariates held at their mean values. There are only 2 observations in observational study category. This is the predicted probabilities in the logit model. For Ologit models, see Table 2-14 in Appendix D.
2. \*: it includes 21 non-R trials and 10 trials (randomization unspecified)

This may suggest that the FDA considers findings from quality design used in postmarketing studies highly when determining label changes. Clinical trials for safety and efficacy produce quality data that could aid physicians prescribe better. Observational studies provide some knowledge about the safety profile of a drug. Some nonclinical studies were for in vitro assay development to support a clinical trial and thus less likely to result in label changes.

Furthermore, the FDA and firms (label updates can be ordered by the FDA or initiated by firms) respond more actively to the findings from required postmarketing studies rather than committed ones. Two scenarios can be considered: (1) more requirements mean that the drug is perceived as “risky” in the first place; thus, the FDA and firms become vigilant; and/or (2) “require” and “being required” makes the FDA and firms pay more attention to the postmarketing information because their responsibility and stakes are higher than commitments.

### **2.4.3.3 Biologics**

The PMR/PMCs associated with biologics ( $p < 0.05$ ) are more likely to result in labeling revision. The logit model tells us that a PMR/PMC for a chemical drug decreases the odds of label

change by 99% (percent change) compared to a biologic drug, holding all others constant ( $z = -2.198$ ,  $p < .05$ ). The difference of predicted probabilities between NDAs and BLAs is much bigger in commitments (94%) than in requirements (22%). And, a large difference between requirements and commitments is observed in NDAs (75%) not in BLAs (3%). These differences were calculated holding other variables constant. See Table 2-18 in Appendix D for further data. The effects of being a biologic on impact level (by the importance of label sections) is also statistically significant. When required, BLAs are more likely to have high impact category of label changes (Table 2-18 in Appendix D).

#### **2.4.3.4 Safety studies**

Although more safety studies (54%) led to label changes compared to non-safety studies (44%) (see Table 2-14 in Appendix D for further details), the effect of studying safety issues seems to be negative when controlling for other variables. But, there is not enough evidence to reject the null hypothesis of the coefficient of safety study being zero at 0.05 level. Also, the odds ratio is small. The sample size is small, and thus a different dataset may yield a statistically significant result.

To examine the role of safety studies on labeling revision, let us look at how many safety studies led to safety label changes and how many efficacy studies led to efficacy label changes. Among 32 FDAAA safety studies, 17 had label changes (53%) while 34 out of 39 AA and PREA studies had efficacy label changes (87%). Among 17 safety PMCs, 6 had safety label changes (35%) and 5 out of 9 efficacy PMCs had label changes (56%). This is consistent with the findings in Section 2.4 that safety studies didn't play a large role in label changes.

Table 2-19 in Appendix D shows the difference in the predicted probabilities of label changes by requirement and safety study (although safety is not statistically significant). This

compares FDAAA safety studies (required, safety) and non-FDAAA safety studies (non-required, safety). In safety studies, FDAAA-safety studies have 87% of predicted probability of label changes while non-FDAAA safety studies have only 6%. But, again, it is not statistically significant, and thus the effect of FDAAA is inconclusive.

#### **2.4.3.5 Expedited approvals and new molecular entities (NMEs)**

The more a drug has expedited program designation (accelerated approval, fast track, and priority review), it is more likely that PMR/PMCs associated with the drug results in labeling revision. The odds of having label changes is 156% higher when there is a unit (the number of expedited program designation) increase. However, this is not statistically significant. When there was no expedited path, 24 out of 48 PMR/PMCs had label changes (50%). For drugs with 1 expedited path, 29% of PMR/PMCs (5 out of 17) had labeling updates: for 2 expedited path designations, 100% (5 out of 5) and for 3 expedited programs, 60% (3 out of 5) had label changes. Among expedited approval paths, accelerated approvals have 100% of label change rate. This is because accelerated approval requires full approval upon the completion of confirmatory trials.

More PMR/PMCs for NMEs resulted in label changes (54%) than PMR/PMCs for non-NMEs (44%). (See Appendix E) However, the effect of NMEs on the probabilities of label changes was statistically insignificant when testing models with NME variable (despite the positive association). I excluded this variable in the estimation of probabilities of label changes. Correlation of NME variable with total number of expedited approval and REMS is high (50%,  $p < .01$  from Pearson's correlation test) and adding NME in the models didn't make much difference.

#### 2.4.3.6 REMS and BBW

The negative effect of REMS on label change and on the impact of label change is somewhat surprising. Having REMS decreases the odds of having label change resulted from PMR/PMCs associated with the drug, but this is statistically insignificant. And, having REMS decreases the odds of having a higher impact level of label change by 95% ( $p < 0.05$ ), controlling for other variables. I hypothesized that a drug with high risk has more likelihood of a label change resulted from PMR/PMCs because postmarketing information about drugs with high risk may be more valuable to share. But, this hypothesis is not supported by data.

REMS was included to capture the perceived risk of a drug. To check this further, I coded serious safety events after approval by using black box warnings. If a drug had any black box warnings after approval, the drug is perceived as riskier. When BBW took place, 75% of postmarketing studies of the drug with BBW had labeling revision and 44% for the drug without BBW.<sup>143</sup> When BBW was added to the statistical model, however, it didn't yield statistical significance.

It may be the difference in the contents of REMS and BBW. The major content of REMS is communication with patients and doctors to reduce medical error and medication guide; the major content of BBW is side effects. Thus, safety events that deserve BBW are more alarming than having REMS.

Another possibility is that REMS may be competing with labels. REMS is again a risk mitigation strategy that involves many communication plans with patients and doctors; this is a function of drug label too. Whether and how they affect each other requires a deeper analysis. The role of REMS and BBW as proxy measures for perceived risk is inconclusive.

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<sup>143</sup> Excluding PREA, with BBW, 9 out of 12 had label changes. Without BBW, 28 out of 63 had labeling change.

#### **2.4.3.7 The number of PMR/PMCs**

Plotting the average percentage of label change by the number of postmarketing studies (Figure 2-7 in Appendix E) doesn't show a clear trend, but we observe a slightly increasing slope when excluding PREA. The number of PMR/PMCs is not statistically significant in predicting probabilities of label change and impact of label change in logit and ologit models. But it has positive association with the three dependent variables.

Figure 2-9 in Appendix E presents the predicted probabilities of label change by the number of PMR/PMCs and by various explanatory variables. Although there are differences in the size of slope and shape of slope, with almost all variables, we see upward slope—upward decreasing marginal effect. This means the total number of PMR/PMCs is positively associated with the likelihood of information updates. This might be attributed to speculations that the marginal effect of PMR/PMCs is low when many PMR/PMCs are attached to drug approvals because not many PMR/PMCs do produce significantly important or new information that could be translated into public health benefit (See Figure 2-5 in Appendix E [CSDD, 2007]).

#### **2.4.3.8 Disease-therapeutic area**

The models show that PMR/PMCs for cardiovascular and diabetes drugs (disease class 3) and psychiatry drugs (disease class 7) are more likely to result in labeling revision ( $p < 0.05$ ). But, this result should be interpreted carefully. The sample size of PMR/PMCs in cardiovascular and diabetes is only 4 for 2 drugs (Trilipix and Welchol). The number of PMR/PMCs in psychiatry drugs in the sample is 5 for 2 drugs (Pristiq and Venlafaxine Hydrochloride). All four drugs are NDAs and most of their postmarketing studies (8 out of 9) are commitments. These two disease classes have higher rate of label change (75% in cardiovascular/diabetes and 80% in psychiatry) (Table 2-15 in Appendix D) and they are statistically significant. But, the sample sizes for these

two classes are too small and all other diseases (all sample sizes > 10) are not statistically significant. Interpretation concerning disease classes is inconclusive.

## **2.5 Discussion and Conclusion**

This paper aimed to shed light on how the FDA utilizes the information acquired in the postmarketing settings. First of all, we observed some effect of PMR/PMCs on market status change but limited effect on REMS requirement. Only one drug (Oforta, NDA) had been discontinued due to the lack of efficacy based on a PMR/PMC and one drug (Avastin, BLA) had a withdrawal of indication based on PMR/PMCs. Postmarketing studies didn't result in further REMS assignment.

Excluding PREA studies, 49% of PMR/PMCs have contributed to label changes. Including PREA, the percentage was higher: 61%. Compared to the BAH 2008 study (51% label change), this number is similar. The BAH study did not include required postmarketing studies—only agreed-upon commitments. The Booz Allen study cohort was 144 studies (out of 224 fulfilled postmarketing studies) and they coded label changes based on FDA interviews. And, it is assumed that the BAH study looked at all label changes, including minor changes—it didn't specify label sections.

As hypothesized, requirement and data quality are positively associated with the predicted probabilities of label change and its impact level with statistical significance. Also, expedited approvals and safety increase the probability of label changes, although this argument lacks statistical significance in the models tested. The unexpected results are the effects of biologics, safety studies, and REMs requirement. PMR/PMCs for biologics have higher probabilities of label



change and higher impact level compared to small molecule drugs. The effect of biologics is dominating the effect of requirement and study design on the probabilities of label change. Also, contrary to expectation, safety and REMS requirement are negatively associated with the predicted probabilities of label change although this is not significant statistically.

With these findings so far, how valuable are postmarketing studies? In Section 2.4.1, we found that drugs with PMR/PMCs are more likely to have label changes, especially important label changes. But, the association was weak or even negative in black box warnings while it was stronger in indication changes. This is somewhat consistent with the findings, in Section 2.4.3, that safety studies did have lower probabilities of label changes and that safety studies are less likely to have safety label changes compared to the rate of efficacy label changes based on efficacy studies.

Lack of role of safety studies on labeling revisions may be supported by the existing literature (Lester et al., 2013; Ishiguro et al., 2012; Wysowski and Schwartz, 2005). The literature showed that spontaneous reports were the primary source of evidence on which FDA's safety communication decisions based. Note that these studies identified spontaneous reports as half (49% - 57%) of the sources of evidence for safety label changes and the other half includes clinical trials, observational studies, animal studies, and others. The researchers did not specify whether those studies are PMR/PMCs established by the FDA, but it is unlikely that the contribution of PMR/PMCs to safety label changes is big (only 1% of all postmarketing studies were based on spontaneous/case reports<sup>144</sup>).

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<sup>144</sup> Among 2,255 PMS established July 2008-May 2016 with study sample information, 24 PMS were analyses based on spontaneous/case reports.

At first glance, these findings sound contradictory: half of postmarketing studies contributed to label changes, but postmarketing studies are not the primary source of evidence for safety label changes according to the existing literature. And this may sound that the role of postmarketing studies on label changes are limited. But, indication and dosage information is very likely to be updated based on PMR/PMCs: spontaneous/case reports are unlikely to yield such information. Since safety labeling revision requires more timely response and it has a wider range from BBW to adverse reaction to medication guide (safety label change could be less impactful—adding a line on adverse reactions is unlikely to have much impact on public health), FDA and sponsors may rely on spontaneous/case reports. The contribution of postmarketing studies may be greater in efficacy-relevant labeling revision than safety labeling revision, but the existing literature dealt with safety labeling revision only.

Let us look at safety label and efficacy label changes separately. Out of 110 PMR/PMCs, 46 had safety label changes (42%) and 50 had efficacy label changes (45%). Among 75 PMR/PMCs excluding PREA studies, 30 had safety label changes (40%) and 20 had efficacy label changes (27%). PREA studies played a large role in updating efficacy labels.

Table 2-27 in Appendix D shows logit model results on safety label changes and efficacy label changes. The role of PMR/PMCs on efficacy labeling revision was larger than the role of PMR/PMCs on safety label changes. The predicted probability of having safety label changes resulting from PMR/PMCs is 39% (N=110, delta-method standard error: 0.058,  $p<0.001$ ) and the probability of having efficacy label changes resulting from PMR/PMCs is 43% (N=110, delta-method standard error: 0.076,  $p<0.001$ ). But, again, excluding PREA studies, the probability of having safety label changes resulting from PMR/PMCs is higher (31%, N=75, delta-method

standard error: 0.09,  $p < .001$ ) than the estimated probability of efficacy label change (14%,  $N = 75$ , delta-method standard error: 0.06,  $p < 0.05$ ).

In sum, the role of PMR/PMCs is larger in efficacy label changes than in safety label changes. Despite the effect of postmarketing studies on efficacy labeling change, the findings on safety labeling revision may create some concerns on the effect of the 2007 FDAAA that authorized the FDA to require firms to study safety issues. I didn't find a statistically significant association between FDAAA studies and label changes. Among non-FDAAA studies, excluding PREA, in this sample, 47% had label changes compared to 53% for FDAAA studies (32 FDAAA studies and 4 AA studies are requirements in the sample). The difference is not significant. This means that we didn't find "safety" effect when "required" effect is controlled. If the FDA still depends on spontaneous reports when issuing safety communications and revising important safety labels, is the current FDAAA safety requirement worth it?

This is an important topic because PMR/PMCs became norm and very costly—one of the reasons why PMR/PMCs deserve attention as a policy issue. CSDD (2003) estimated that a PMR costs \$3.7 million on average and HHS reported that conducting a postmarketing trial costs \$20 million<sup>145</sup> on average (Sertkaya et al., 2014).<sup>146</sup> In the sample of postmarketing studies for drug approvals in 2008, the estimated total cost of 36 fulfilled FDAAA safety requirements, excluding 6 in-vitro and genotypic/phenotypic analyses, would be \$683 million (see Table 2-26 in Appendix D for the cost estimation). So the benefit would need to be at least equal to the cost.

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<sup>145</sup> <http://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>

<sup>146</sup> Furthermore, postmarketing studies and trials can be a burden on small and mid-size pharmaceutical and biomedical firms, and this may result in decrease in drug innovation (Collier, 2009). And, FDA's regulatory costs (regulating PMR/PMCs) could be significant: FDA budget for postmarket safety oversight was \$211 million for FY 2013, including an increase of \$23 million from FY 2012. Note that FDA budget for postmarket safety oversight includes all activities for postmarket safety oversight; how much of it is spent on PMR/PMCs is unidentified. <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM291555.pdf>

We might want to probe what kinds of improvements in labeling would be needed to generate benefit of that scale. Perhaps, expanding the use of a drug to patients who would have not been treated without the drug (by adding new indication) and save lives from life-threatening side effects of a drug (by withdrawing/discontinuing or adding strong warning such as BBW) could scale up the benefit of labeling revision. Among those 36 fulfilled FDAAA requirements, 14 studies led to label changes, 12 studies didn't lead to label changes, and label change was undetermined for 10 studies. Among those 14 studies that resulted in labeling revision, there was 1 indication change and zero BBW change. No drug was withdrawn or discontinued based on FDAAA safety requirements.

Also, one might argue that it's a choice between approval with postmarketing studies and delayed approval (with pre-approval studies). In this trade-off scenario, if a drug is approved with postmarketing study option, the cost of having postmarketing studies can be justified when the cost is equal to or smaller than the sum of cost of delaying approval and pre-approval studies. The costs of studies and delaying approval depend on many variables (the length/size/design of the studies, drug target population size, length of delay of approval, and drug price). But, it is accepted that the cost of delaying approval is sufficiently large—e.g., drug lag debate and the pediatric study incentives (6 months of additional marketing exclusivity).

In this paper, I do not attempt to measure the benefit of a label change or early approval, but thinking about justifying the cost of postmarketing studies can facilitate a further discussion on cost and benefit of postmarketing studies.

Finally, lack of enforcement of PMR/PMCs has been a part of important policy debates because enforcement is crucial for realizing the benefit of PMR/PMCs. Out of total 202

postmarketing studies established in 2008, 40% are unfulfilled.<sup>147</sup> Among 14 delayed or pending studies, 86% were postmarketing requirements (3 AA studies, 8 PREA studies, 1 FDAAA safety requirement, and 2 PMCs).

Among 53 released studies, 32 studies (60%) are PREA requirements, 13 are postmarketing commitments, 7 are FDAAA requirements, and 1 is accelerated approval requirement. According to the FDA, it informs the applicant that a study has been released from its requirement/commitment because it is either no longer feasible or would no longer provide useful information. But, I found more diverse reasons for releasing PMR/PMCs in my dataset. The following reasons are found in this dataset<sup>148</sup>: (1) sponsors do not seek indications<sup>149</sup>; (2) sponsors do not plan to complete the study<sup>150</sup>; (3) sponsors plan to withdraw their drugs<sup>151</sup>; (4) the study does not provide useful information<sup>152</sup>; and (5) a PMR/PMC is replaced with a new PMR/PMC.<sup>153</sup>

In conclusion, slightly less than a half of fulfilled PMR/PMCs in the sample, excluding PREA, resulted in meaningful label changes. One suggestion is that decisions about label changes

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<sup>147</sup> The current status of 13 studies are unknown as of April 2018. Out of 202 studies, 7 are delayed, 7 are pending, 13 are ongoing, and 53 studies had been released as of April 2018 (40%). The rest 60% were fulfilled

<sup>148</sup> FDA rarely shares the rationale for releasing PMR/PMCs with the public. Most of time, FDA sends a letter to the sponsor separately from approval letters. For NDA #22159, FDA sent a letter to the sponsor on 3/17/2016 to inform a PREA study was released when there was an approval on 3/18/2016 which contains fulfillment information.

<sup>149</sup> In approval letter, “with removal of the SAD indication from the approved Luvox CR labeling, you are not permitted to promote the drug for this indication. As described in a letter issued separately today, you are released from the PREA and maintenance study requirements associated with the SAD indication.”

<sup>150</sup> “NDA WD 06/28/2012. Applicant does not plan to complete any of the studies that were initiated. Per letter dated 3/14/2017, this study was released” FDA PMR/PMC database comments on status. NDA #22244 Lusedra had four PREA study requirements.

<sup>151</sup> FDA terminated a PMC and then released it. “On January 31, 2013, the sponsor submitted a request to withdraw their NDA” FDA says.

<sup>152</sup> A study to assess maternal plasma and breast milk so as to estimate potential infant exposure was released according to the FDA: “You are released from the above commitment to conduct a milk/plasma type lactation study as lactation does not change maternal physiology enough to significantly alter drug pharmacokinetics in most situations.”

<sup>153</sup> For NDA 22159, the original PREA requirement was for age group 2-6. This PMR was released on 3/17/2016. But, 3/18/2016 approval letter says that its PREA requirement was fulfilled for age group 3-6 and the sponsor fulfilled all requirement. The study descriptions for both 3-6 age group and 2-6 group are exactly same except for the age group.

can be a part of postmarketing study cycle. The current lifecycle of PMR/PMCs ends with designating study status as “fulfilled,” “terminated,” or “released” after firms’ submission of reports to the FDA. After the finalized status (fulfilled, terminated, or released), FDA can add “regulatory action” status to determine whether and what regulatory actions might be needed.

Another recommendation is that FDA aims to receive information that could potentially have big impact on public health when establishing FDAAA safety requirements. Furthermore, more detailed postmarketing study descriptions and enhanced data transparency are needed (Wallach et al., 2018; Sharfstein and Stebbins, 2017), especially for study final reports and the basis of decisions on labeling revision.

### **Limitations**

This paper has limitations. Matching a PMR/PMC with its effect on postmarketing actions required considerable searching with keywords (study phase, drug name, intervention, population, etc.) and reading all labels and approval letters associated with the drugs. Since there is no identification for linking up a postmarketing study with regulatory actions, sometimes this matching required judgment calls. To reduce errors and bias, I performed the coding process twice and followed coding rules that are more specifically addressed in Section 2.3.3 and in Appendix G.

In addition, the regulatory effect of postmarketing studies can be further confirmed when we look at the results of postmarketing studies. Although the results of PMR/PMCs are not included in this paper, I find that label updates, in general, reflected PMR/PMC results (i.e. a drug may be dangerous in a specific subpopulation, a dose is too high, a drug requires more attention when administered, etc.). In theory, controlling for the PMR/PMC results can help us confirm our

findings. But, examining PMR/PMC results in further detail and measuring them is difficult and it is out of scope.

Moreover, the value of information acquired through PMR/PMCs may not be limited to label changes. Information dissemination among health care community can be achieved through publishing studies in professional journals or through FDA's safety communication. Assessing the effects of PMR/PMCs in publications and FDA's communication will deepen understanding of the value of PMR/PMCs in the future.

Along the same line, information is not limited to label changes or market status changes. A further issue is whether and how much there are values of postmarketing studies that confirm priori assumptions without changing labels. Confirming findings may still have value if they lead various parties to change their behavior. Perhaps some clinicians were still skeptical about a drug, but the results of the postmarketing studies convinced them to accept the worth of the drug. Or some educated/informed patients may be more willing to take a drug that was doubted. And, payers would be more willing to pay for the drugs with confirming evidence on safety and effectiveness. But, these are not fully captured by label or market status changes. This would require further examinations on behavioral changes of payers, clinicians, and patients.

Another avenue for thinking about the value of postmarketing studies is FDA's learning. Is it possible that postmarketing studies could increase FDA's understanding when studies are likely to provide useful information? That information could help the FDA decide when postmarketing requirements and commitments will be the most useful. Again, however, this requires more analyses on FDA's establishing, monitoring, and managing postmarketing studies. These analyses are out of scope of this study.

On the other hand, postmarketing requirements and commitments are not the only source that provides meaningful clinical data and information. One might raise a question that there might be a vast disconnect between PMR/PMCs and good clinical population research in the United States. May (2019) found a clear trend in clinical testing: “clinical trials are getting more complicated....more specificity and complexity in the launch of a study, details of the procedures, and methods of tracking progress and interpreting outcomes.” Without alignment and coordination between FDA’s PMR/PMCs and other research, the value of studies might be diminished. Ken Getz, director of sponsored programs at the Tufts Center for the Study of Drug Development, says testing similar drugs with similar hypotheses in different clinical trials “can result in wasted resources and can increase the odds of false-negative results.” Examination of this problem is out of scope for this study.

Finally, the sample size is not big enough to see meaningful differences among drug classes, study purposes, and expedited programs.



## Bibliography for Study 2

- Avorn, J. (2004). *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs*, 108. New York, N.Y. Knopf.
- Bakke, O. M., Manocchia, M., Abajo, F., Kaitin, K. I., & Lasagna, L. (1995). Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: a regulatory perspective. *Clinical Pharmacology & Therapeutics*, 58(1), 108-117.
- Booz Allen Hamilton. (2008). Independent Evaluation of FDA's Prescription Drug User Fee Act – Evaluations and Initiatives; CDER Technical Support and Analysis -- Final Report on the PMR/PMC Backlog Review. Retrieved from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM181135.pdf>
- Brewer, T., & Colditz, G. A. (1999). Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *Jama*, 281(9), 824-829.
- Carpenter, D., Chernew, M., Smith, D. G., & Fendrick, A. M. (2003). Approval times for new drugs: does the source of funding for FDA staff matter?. *Health Affairs*, W3.
- Carpenter, D. P. (2004). The political economy of FDA drug review: Processing, politics, and lessons for policy. *Health Affairs*, 23(1), 52-63.
- Carpenter, D., Zucker, E. J., & Avorn, J. (2008). Drug-review deadlines and safety problems. *New England Journal of Medicine*, 358(13), 1354-1361.
- Collier, R. (2009). Rapidly rising clinical trial costs worry researchers. *Canadian Medical Association Journal*, 180(3), 277-278.
- CSDD, Kaitin KI, editor. FDA requested postmarketing studies in 73% of recent new drug approvals. Tufts Center for the Study of Drug Development Impact Report. 2004 July/August;6(4)
- CSDD, Kaitin KI, editor. Challenges loom for postmarketing study commitments; benefits unclear. Tufts Center for the Study of Drug Development Impact Report. 2007 May/June;9(3)
- CSDD, Kaitin KI, editor. Postmarketing studies are becoming the norm in U.S., Europe, and Japan. Tufts Center for the Study of Drug Development Impact Report. 2008 July/August;10(4)
- Downing, N. S., Aminawung, J. A., Shah, N. D., Braunstein, J. B., Krumholz, H. M., & Ross, J. S. (2012). Regulatory review of novel therapeutics—comparison of three regulatory agencies. *New England Journal of Medicine*, 366(24), 2284-2293.

- Downing, N. S., Shah, N. D., Aminawung, J. A., Pease, A. M., Zeitoun, J. D., Krumholz, H. M., & Ross, J. S. (2017). Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *Jama*, 317(18), 1854-1863.
- Downing, N. S., Zhang, A. D., & Ross, J. S. (2017). Regulatory Review of New Therapeutic Agents—FDA versus EMA, 2011–2015. *New England Journal of Medicine*, 376(14), 1386-1387.
- Dusetzina, S. B., Higashi, A. S., Dorsey, E. R., Conti, R., Huskamp, H. A., Zhu, S., ... & Alexander, G. C. (2012). Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Medical care*, 50(6), 466.
- Fan, Y., Sun, B., Agarwal, S., & Zhang, L. (2016). Review of Transporter-Related Postmarketing Requirement or Postmarketing Commitment Studies. *The Journal of Clinical Pharmacology*, 56(S7).
- US Food and Drug Administration (2004). Innovation or stagnation. Challenge and Opportunity on the Critical Path to New Medical Products. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf>
- US Food and Drug Administration (2011). Guidance for industry: postmarketing studies and clinical trials—implementation of §505(o)(3) of the Federal Food, Drug, and Cosmetic Act (April 2011). Retrieved from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.
- US Food and Drug Administration (2007). Guidance: Drug Safety Information – FDA’s Communication to the Public. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072281.pdf>
- US Food and Drug Administration (2009). Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>
- US Food and Drug Administration (2012). Guidance: Drug Safety Information – FDA’s Communication to the Public. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf>
- US Food and Drug Administration (2013). Guidance for Industry: Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act. CDER and CBER, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>

- US Food and Drug Administration (2013). Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need; Public Hearing. <http://www.fda.gov/Drugs/NewsEvents/ucm335680.htm>
- US Food and Drug Administration (2015). White Paper: FDA and Accelerating the Development of the New Pharmaceutical Therapies. <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM439183.pdf>
- Fontanarosa, P. B., Rennie, D., & DeAngelis, C. D. (2004). Postmarketing surveillance—lack of vigilance, lack of trust. *Jama*, 292(21), 2647-2650.
- United States General Accounting Office (GAO). (1996) Testimony Before the Subcommittee on Health and Environment, Committee on Commerce, House of Representatives. FDA REVIEW TIMES.
- Gibbons, R. D., Brown, C. H., Hur, K., Marcus, S. M., Bhaumik, D. K., Erkens, J. A., ... & J John Mann, M. D. (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*.
- Glasser, S. P., Salas, M., & Delzell, E. (2007). Importance and Challenges of Studying Marketed Drugs: What Is a Phase IV Study? Common Clinical Research Designs, Registries, and Self-Reporting Systems. *The Journal of Clinical Pharmacology*, 47(9), 1074-1086.
- Grabowski, H. G., & Vernon, J. M. (1983). *The Regulation of Pharmaceuticals: Balancing the Benefits and the Risks*. Washington, D.C.: American Enterprise Institute.
- Grabowski, H. G., & Wang, Y. R. (2006). The quantity and quality of worldwide new drug introductions, 1982–2003. *Health Affairs*, 25(2), 452-460.
- Grabowski, H., & Wang, Y. R. (2008). Do faster Food and Drug Administration drug reviews adversely affect patient safety? An analysis of the 1992 Prescription Drug User Fee Act. *Journal of Law and Economics*, 51(2), 377-406.
- Harvey, C., Lumley, C. E., & Walker, S. R. (1993). A comparison of the review of a cohort of NCEs by four national regulatory authorities. *Journal of Pharmaceutical Medicine*, 3, 65-65.
- Hollingsworth, K., Romney, M. C., Crawford, A., & McAna, J. (2015). Risk evaluation mitigation strategy: impact of application of the Food and Drug Administration's strategy on use of erythropoiesis-stimulating agents and transfusion in patients with chemotherapy-induced anaemia. *Journal of clinical pharmacy and therapeutics*, 40(3), 299-303.
- Hollingsworth, K., Romney, M. C., Crawford, A., & McAna, J. (2016). The impact of the risk evaluation mitigation strategy for erythropoiesis-stimulating agents on their use and the incidence of stroke in medicare subjects with chemotherapy-induced anemia with lung and/or breast cancers. *Population health management*, 19(1), 63-69.

- Institute of Medicine (2007). *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice, Institute of Medicine.
- Ishiguro, C., Hall, M., Neyarapally, G. A., & Dal Pan, G. (2012). Post-market drug safety evidence sources: an analysis of FDA drug safety communications. *Pharmacoepidemiology and drug safety*, 21(10), 1134-1136.
- Kaitin, K. I., Mattison, N., Northington, F. K., & Lasagna, L. (1989). The drug lag: an update of new drug introductions in the United States and in the United Kingdom, 1977 through 1987. *Clinical Pharmacology & Therapeutics*, 46(2), 121-138.
- Karpel, J. P., Peters, J. I., Szema, A. M., Smith, B., & Anderson, P. J. (2009). Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting  $\beta$ -agonists. *Annals of Allergy, Asthma & Immunology*, 103(4), 304-310.
- Kesselheim, A. S., Wang, B., Franklin, J. M., & Darrow, J. J. (2015). Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ* 2015;351:h4633.
- Kesselheim, A. S., & Darrow, J. J. (2015). FDA designations for therapeutics and their impact on drug development and regulatory review outcomes. *Clinical Pharmacology & Therapeutics*, 97(1), 29-36.
- Kramer, D. B., Xu, S., & Kesselheim, A. S. (2012). Regulation of medical devices in the United States and European Union.
- Lester, J., Neyarapally, G. A., Lipowski, E., Graham, C. F., Hall, M., & Dal Pan, G. (2013). Evaluation of FDA safety-related drug label changes in 2010. *Pharmacoepidemiology and drug safety*, 22(3), 302-305.
- Mattison, N., & Richard, B. W. (1987). Postapproval Research Requested by the FDA at the Time of NCE Approval, 1970–1984. *Drug Information Journal*, 21(3), 309-329.
- May, M. (2019). Twenty-five ways clinical trials have changed in the last 25 years.
- Mostaghim, S. R., Gagne, J. J., & Kesselheim, A. S. (2017). Safety related label changes for new drugs after approval in the US through expedited regulatory pathways: retrospective cohort study. *bmj*, 358, j3837.
- Naci, H., Smalley, K. R., & Kesselheim, A. S. (2017). Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *Jama*, 318(7), 626-636.

- Office of Inspector General (1996). Postmarketing Studies of Prescription Drugs. U.S. Department of Health and Human Services. May 1996. OEI-03-94-00760.
- Office of Inspector General (2006). FDA's Monitoring of Postmarketing Study Commitments. U.S. Department of Health and Human Services. June 2006. OEI-01-04-00390.
- Pease, A. M., Krumholz, H. M., Downing, N. S., Aminawung, J. A., Shah, N. D., & Ross, J. S. (2017). Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ*, 357, j1680.
- Peltzman, S. (1972). The benefits and costs of new drug regulation. University of California.
- Peltzman, S. (1974). Regulation of pharmaceutical innovation: The 1962 amendments. *American Enterprise Institute for Public Policy Research*, 15
- Psaty, Bruce. (2004). Public Witness. FDA, Merck, and Vioxx: Putting Patient Safety First? Hearing before the Committee on Finance. United States Senate. One Hundred Eighth Congress Second Session.
- Roberts, S. A., Allen, J. D., & Sigal, E. V. (2011). Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe. *Health affairs*, 30(7), 1375-1381.
- Sarpatwari, A., Franklin, J. M., Avorn, J., Seeger, J. D., Landon, J. E., & Kesselheim, A. S. (2015). Are Risk Evaluation and Mitigation Strategies Associated With Less Off-Label Use of Medications? The Case of Immune Thrombocytopenia. *Clinical Pharmacology & Therapeutics*, 97(2), 186-193.
- Sertkaya, A., Birkenbach, A., Berlind, A., & Eyraud, J. (2014). Examination of clinical trial costs and barriers for drug development. Report, US Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Washington, DC.
- Slomiany, M., Bitar, R., Kruse, S., Jeffers, S., Berkowitz, K., & Hassan, M. (2015). Drug Safety and the Cost of Monitoring: The Role of REMS in Risk Management. *Therapeutic Innovation & Regulatory Science*, 49(4), 514-523.
- Steenburg, C. (2006). Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule, The. *Food & Drug LJ*. Retrieved from [http://heinonlinebackup.com/hol-cgi-bin/get\\_pdf.cgi?handle=hein.journals/foodlj61&section=23](http://heinonlinebackup.com/hol-cgi-bin/get_pdf.cgi?handle=hein.journals/foodlj61&section=23)
- Van Norman, G. A. (2016). Drugs and devices: comparison of European and US approval processes. *JACC: Basic to Translational Science*, 1(5), 399-412.
- Wardell, W. M. (1974). Therapeutic implications of the drug lag. *Clinical Pharmacology & Therapeutics*, 15(1), 73-96.
- Wardell, W. (1978). A Close Inspection of the 'Calm Look'. *JAMA*, 239(19), 2004-2011.

- Wardell, W.M. (1978). The drug lag revisited: Comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976. *Clinical Pharmacology & Therapeutics*, 24, 499–524.
- Wardell, W. (1979). Rx: More Regulation or Better Therapies. *Regulation*, 3.
- Wardell, W. M., and L. Lasagna. (1975). *Regulation and Drug Development*. Washington, D.C.: American Enterprise Institute for Public Policy Research.
- Sharfstein, J. M., & Stebbins, M. (2017). Enhancing transparency at the US Food and Drug Administration: moving beyond the 21st Century Cures Act. *Jama*, 317(16), 1621-1622.
- Sidney M. Wolfe and Larry D. Sasich. (2002). Public Citizen Health Research Group. FDA Hearing on Risk Management of Prescription Drugs
- Woloshin, S., M.D., Schwartz, L. M., M.D., White, B., B.A., & Moore, T. J., A.B. (2017). The fate of FDA postapproval studies. *The New England Journal of Medicine*, 377(12), 1114-1117.
- Wysowski, D. K., & Swartz, L. (2005). Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Archives of internal medicine*, 165(12), 1363-1369.

## Appendix D for Study 2: Tables

**Table D-12. Sources of evidence for safety label changes in 2010**

See Table 1 in Lester, J., Neyarapally, G. A., Lipowski, E., Graham, C. F., Hall, M., & Dal Pan, G. (2013). Evaluation of FDA safety-related drug label changes in 2010. *Pharmacoepidemiology and drug safety*, 22(3), 302-305.

**Table D-13. Frequency analysis of drug safety communications by evidence source**

See Table 1 in Ishiguro, C., Hall, M., Neyarapally, G. A., & Dal Pan, G. (2012). Post-market drug safety evidence sources: an analysis of FDA drug safety communications. *Pharmacoepidemiology and drug safety*, 21(10), 1134-1136.

**Table D-14. Predicted probabilities, by requirement and design**

	No label change	Low impact	High impact
Required			
RCT	0.053	0.704	0.242
Non-RCT	0.361	0.608	0.031
Observational	0.816	0.18	0.004
Nonclinical	0.426	0.55	0.024
Committed			
RCT	0.324	0.639	0.036
Non-RCT	0.828	0.168	0.004
Observational	0.974	0.025	0
Nonclinical	0.864	0.133	0.003
Change from "required" to "committee"			
RCT	-0.271	0.065	0.206
Non-RCT	-0.467	0.44	0.027
Observational	-0.158	0.155	0.004
Nonclinical	-0.438	0.417	0.021

**Table D-15. Label changes by disease, excluding PREA**

Drug-disease class	Label Change	No label change	Total
1 Autoimmune, musculoskeletal, dermatology	9 (69%)	4	13
2 Cancer and hematology	9 (64%)	5	14
3 Cardiovascular and diabetes	<b>3 (75%)</b>	<b>1</b>	<b>4</b>
4 Genitourinary and renal	-	-	-
5 Infectious disease	5 (42%)	7	12
6 Neurology	2 (13%)	13	15
7 Psychiatry	<b>4 (80%)</b>	<b>1</b>	<b>5</b>
8 Other	5 (42%)	7	12
Total	37 (49%)	38	75

**Table D-16. Label changes by FDA office/division, excluding PREA**

FDA Office/Division	Label Change	No label change	Total
ODE I	6 (30%)	14	20
ODE II	4 (44%)	5	9
ODE III	5 (45%)	6	11
Antimicrobial	5 (42%)	7	12
Hematology/Oncology	17 (74%)	6	23
Total	37 (49%)	38	75

**Table D-17. Model test results**

Tests		Model 1	Model 2	Model3
Wald	Chi2	13.63	18.79	17.57
	Prob>Chi2	0.0181	0.0045	0.0074
Likelihood ratio	Chi2	57.04	71.27	72.66
	Prob>Chi2	0.0000	0.0000	0.0000

A significant test statistic provides evidence that the parallel regression assumption has been violated. The insignificant overall chi-square value (given in the row labeled All) suggests that ologit's assumptions are met.



## Impact and Impact2 ologit models brant test

Brant test of parallel regression assumption

	chi2	p>chi2	df
All	7.72	0.358	7
total_pms	0.21	0.648	1
required	1.82	0.177	1
design3	2.52	0.112	1
nda_bla	2.72	0.099	1
total_exp	0.31	0.579	1
safety	0.07	0.789	1
disease2	1.22	0.269	1

Brant test of parallel regression assumption

	chi2	p>chi2	df
All	7.95	0.337	7
total_pms	0.05	0.822	1
required	0.04	0.841	1
design3	0.49	0.484	1
nda_bla	0.00	0.996	1
total_exp	2.31	0.128	1
safety	0.00	0.996	1
disease2	0.30	0.583	1

Brant test of parallel regression assumption

	chi2	p>chi2	df
All	7.45	0.488	8
total_pms	0.10	0.753	1
required	2.70	0.100	1
design3	2.31	0.129	1
disease2	0.73	0.393	1
nda_bla	1.34	0.247	1
safety	0.00	0.989	1
total_exp	0.61	0.433	1
total_rems	0.05	0.818	1

Brant test of parallel regression assumption

	chi2	p>chi2	df
All	14.00	0.082	8
total_pms	0.09	0.764	1
required	0.48	0.487	1
design3	1.02	0.312	1
disease2	0.41	0.524	1
nda_bla	0.00	0.998	1
safety	0.00	0.998	1
total_exp	1.42	0.233	1
total_rems	2.26	0.132	1

## Collinearity test results

Variable	VIF	SQRT VIF	Tolerance	R- Squared
total_pms	1.53	1.24	0.6536	0.3464
design3	1.41	1.19	0.7089	0.2911
disease2	1.65	1.28	0.6063	0.3937
required	2.02	1.42	0.4939	0.5061
nda_bla	1.74	1.32	0.5731	0.4269
total_exp	1.59	1.26	0.6274	0.3726
rems_2008	1.81	1.34	0.5529	0.4471
safety	1.56	1.25	0.6428	0.3572
Mean VIF	1.66			

	Eigenval	Cond Index
1	6.2874	1.0000
2	0.8898	2.6582
3	0.7794	2.8402
4	0.3975	3.9770
5	0.2461	5.0546
6	0.1561	6.3470
7	0.1217	7.1874
8	0.0770	9.0333
9	0.0450	11.8243

Condition Number 11.8243

Eigenvalues & Cond Index computed from scaled raw sscp (w/ intercept)

Det(correlation matrix) 0.1424

**Table D-18. Predicted probabilities, by NDA-BLA and requirement**

	No change	Low impact	High impact
Required			
NDA	0.435	0.542	0.023
BLA	0.004	0.188	0.808
NDA - BLA	0.431	0.354	-0.785
Committed			
NDA	0.868	0.129	0.003
BLA	0.035	0.634	0.33
NDA - BLA	0.833	-0.505	-0.327
Change from required to committed			
NDA	-0.433	0.413	0.02
BLA	-0.031	-0.446	0.478

Note: Ordered logit model with impact.

	Pr (y)
Average	0.548
required NDA	0.778
required BLA	1.000
non-required NDA	0.031
non-required BLA	0.970

Note: Logit model

**Table D-19. Predicted probabilities, by requirement and safety**

	Required	Non-required	Difference
Safety studies	0.870	0.057	0.813
Non-Safety studies	0.982	0.337	0.645
Difference	0.112	0.280	-

Notes: other covariates held at their mean values. There are only 2 observations in observational study category. Safety, required studies are FDAAA studies and non-safety, required studies are accelerated approval confirmatory studies.

**Table D-20. Variable descriptions**

Variable name	Variable description
Label_change	Whether or not a label was changed 1: label changed 0: label not changed
Impact_Group	0: No impact—no label change 1: sections 6-8 (adverse reaction, drug interaction, subpopulation) 2: sections 0-5 (BBW, indication, dosing, contraindication, warning)
Required	Whether or not a postmarketing study is required 1: required 0: committed
NME	1: NME 0: Non-NME

Variable name	Variable description
505(b) application type <sup>154</sup>	1: 505(b)(1) 2: 505(b)(2)
Total_expd	Total number of expedited programs applied for the drug
Expedited	1: Expedited 0: Traditional
Expedited2	1: AA or FT approval 0: Priority or Traditional approval
Orphan	1: Orphan 0: Non-orphan
Study	Whether or not this constitutes as "study" 1: Study 0: Not a study
Clinical	Whether this PMR/PMC is clinical 1: clinical 0: non-clinical
Trial	Whether this PMR/PMC is a trial 1: Trial 0: Non-trial
Data_Type (Design2)	Types of data used in a postmarketing study 3: Clinical trial 2: Observational 1: Nonclinical
Design	Design of postmarketing study 1: RCT 2: non-R trial 3: Observational 4: Assay/In Vitro 5: Nonclinical 6: Data/analysis 7: Other
Safety study	1: Safety study 0: Non-safety study
Study Type	1: Clinical Safety 2: Clinical Efficacy 3: Clinical Pharmacology 4: Nonclinical toxicology 5: Microbiology 6: Immunogenicity

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<sup>154</sup> A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). A 505(b)(1) application is full application.

Variable name	Variable description
Purpose	Purpose of a postmarketing study 1: Safety and Efficacy, general 2: Safety, general 3: Efficacy, general 4: Pharmacology, general 5: Dose optimization 6: Drug interaction 7: Subpopulation 8: Nonclinical toxicology 9: Immunogenicity/Virology 10: Other
Total_PMS	Total number of postmarketing studies assigned to a drug (between July 2008 and July 2015)
REMS	1: REMS 0: no REMS
BBW	1: BBW 0: no BBW
Efficacy	Whether or not a postmarketing study is required/committed for validating, confirming, and satisfying efficacy issues
Disease2	Disease area code 1: autoimmune, musculoskeletal, and dermatology 2: cancer and hematology 3: cardiovascular disease, diabetes, and hyperlipidemia 4: genitourinary and renal 5: infectious disease 6: neurology 7: psychiatry 8: other
FDA office	Division/Office 1: Antimicrobial 2: Hematology/Oncology 3: ODE I 4: ODE II 5: ODE III
Drug ratings	Continuous variable. Combined the following ratings: Drugs.com, askapatient.com, drugratingz.com I scaled them to 5 and averaged (5 the highest rating, 1 the lowest rating)

**Table D-21. Drugs with label changes, by the existence of PMR/PMCs**

	BBW and/or Indication change		Total
	Yes	No	
Yes PMR/PMCs	36 (71%)	15	51
No PMR/PMCs	8 (31%)	18	26
Total	44 (57%)	33	77

Notes: 2008 drug-approval v2 data. 2008 new drug approval and PMS or no-PMS. And, whether any BBW or indication change was made is identifiable.

**Table D-22. Drugs with label changes, by BBW and Indication changes**

	BBW change			Indication change		
	Yes	No	total	Yes	No	total
Yes PMR/PMCs	12 (21%) (75%)	44	56	31 (61%) (84%)	20	51
No PMR/PMCs	4 (13%) (25%)	26	30	6 (24%) (16%)	19	25
total	16	70	86	37	39	76

Notes: the percentage in the first row is the row percentage and the percentage in the second row is the column percentage. For the drugs with postmarketing studies, 21% of them had label change on BBW (12 out of 56) while 13% of drugs without postmarketing studies (4 out of 30) had label change on BBW. Among drugs that had label change on BBW, 75% (12 out of 16) had postmarketing studies.

**Table D-23. Drugs with label changes, by fulfilled vs. unfulfilled PMR/PMCs**

PREA	Fulfilled vs. unfulfilled	BBW and/or Indication change		Total
		Yes	No	
Incl. PREA	Only fulfilled studies	17 (65%)	9	26
	Only unfulfilled studies	12 (57%)	9	21
Excl. PREA	Only fulfilled studies	20 (74%)	7	27
	Only unfulfilled studies	6 (75%)	2	8

Note: In the sample, for drugs with only unfulfilled postmarketing studies, 3 of 24 had no information on indication. Same for the sample excluding PREA studies.

**Table D-24. Logit/Ologit models with study of purpose**

	label_change	impact	impact2
main			
total_pms	0.974 (-0.07)	0.954 (-0.20)	1.040 (0.18)
required	35264.3* (2.54)	63.31** (3.28)	289.1*** (3.53)
1bn.design3	. .	. .	. .
2.design3	0.0100* (-2.24)	0.0345** (-2.98)	0.136 (-1.92)
3.design3	0.0000162* (-2.55)	0.00182** (-2.60)	0.00278* (-2.55)
4.design3	0.0195* (-1.98)	0.0401** (-3.14)	0.112* (-2.18)
1bn.disease2	. .	. .	. .
2.disease2	0.128 (-1.15)	0.172 (-1.41)	0.198 (-1.27)
3.disease2	245745.5** (2.62)	236.5** (2.67)	194.0** (2.63)
5.disease2	3.089 (0.70)	0.366 (-0.73)	0.860 (-0.11)
6.disease2	6.051 (0.34)	14.34 (1.66)	0.791 (-0.14)
7.disease2	92843.3* (2.45)	664.6** (3.15)	276.6** (3.01)
8.disease2	3.039 (0.45)	0.640 (-0.29)	1.286 (0.17)
nda_bla	0.00000804** (-2.60)	0.000202*** (-3.75)	0.00118*** (-3.43)
total_exp	36.57* (2.16)	6.148* (2.20)	7.796** (2.67)
rems_2008	0.0000466* (-2.20)	0.00218*** (-3.63)	0.0101** (-2.77)
1bn.purpose	. .	. .	. .
2.purpose	7.535 (0.73)	0.503 (-0.56)	13.22 (1.71)
3.purpose	1228.3* (2.16)	20.31 (1.84)	50.84* (2.25)
4.purpose	4433.3 (1.93)	30.80* (1.99)	50.76* (2.20)
N	75	75	75

**Table D-25. Label changes, comparing drugs with PMR/PMCs to drugs without PMR/PMCs (new drug approvals 2008-2010)**

	With PMR/PMC	Without PMR/PMC	Total
Label changed	157 (93%)	72 (75%)	229
No label changed	11 (7%)	24 (25%)	35
Total	168	96	264

Notes:

1. The sample includes all new drugs approved between 2008 and 2010. Labeling revision supplemental approvals (including efficacy and other supplemental approvals, excluding Chemistry, Manufacturing, and Controls (CMC) and REMS revisions) after original approval until June 1, 2018 were identified.
2. The dataset was linked to PMR/PMC data.
3. The sample excludes 22 drug approvals: 18 drug approvals that have no further information on label changes or PMR/PMCs, and 4 drugs that had two original approvals (the earlier original approval was granted before 2008)

**Table D-26. Cost estimation of FDAAA studies**

Study type	Subtype	Cost per study	Cost after inflation rate adj. (2018)
Trials <sup>1</sup>	Oncology (5)	\$38.9M	
	Gastrointestinal (6)	\$21.8M	
	Neurology (4)	\$14.1M	
	Pulmonary (1)	\$72.9M	
	Anal (2)	\$32.1M	
	Hematology (2)	\$27M	
	Imaging (2)	\$20M	
	Subtotal		\$613M (+6.82%) → \$655M
Observational <sup>2</sup>	5-years obs. (3)	\$2.25M	
	Registry—indefinitely (1)	\$4M	
	Observational study—length not specified, but using large secondary data (1)	\$175K	
	Subtotal		\$11M (+17.87%) → \$13M
In-vitro, nonclinical studies	Nonclinical (9) In-vitro (5)	\$1.5M No reference	\$14M (+8.55%) → \$15M
Other	Annual genotypic and phenotypic analyses (1)	No reference	

Notes:

1. Average cost estimation by disease class is based on 2014 HHS study (file:///E:/Box/Literature/20-20Since20Sep202015/Cost20of20Phase20420(Postmarketing)/Cost20of20drug20development20-20HHS202014.pdf)
2. The average cost of observational and registry study is from 2009 study (<https://collections.nlm.nih.gov/master/borndig/101507734/first20look20at20the20volume20and20cost20of20comparative20effectiveness20research20in20the20United20States.pdf>)
3. Average nonclinical toxicology study cost is from 2013 CSDD study ([https://www.contractpharma.com/issues/2013-06/view\\_features/characterizing-the-cost-of-non-clinical-development-activity](https://www.contractpharma.com/issues/2013-06/view_features/characterizing-the-cost-of-non-clinical-development-activity))

4. According to the Bureau of Labor Statistics consumer price index, prices in 2018 are 6.82% higher than prices in 2014.
5. According to the Bureau of Labor Statistics consumer price index, prices in 2018 are 8.55% higher than prices in 2013.
6. According to the Bureau of Labor Statistics consumer price index, prices in 2018 are 17.87% higher than prices in 2009.



**Table D-27. Logit model results – safety label change vs. efficacy label change including PREA studies**

**(N=110)**

	(1) safety_label	(2) efficacy_l~l
main		
total_pms	0.893 (-0.77)	0.891 (-0.66)
required	7.363** (2.89)	36.14*** (3.99)
1bn.design3	.	.
2.design3	0.309 (-1.88)	0.791 (-0.30)
3.design3	0.0733* (-2.20)	1.968 (0.59)
4.design3	0.140** (-2.94)	0.0784** (-3.07)
1bn.disease2	.	.
2.disease2	3.564 (1.22)	1.873 (0.55)
3.disease2	198.3** (3.03)	58.95 (1.68)
5.disease2	2.292 (0.89)	4.796 (1.39)
6.disease2	5.863 (1.68)	26.31* (2.13)
7.disease2	31.59** (2.87)	178.8** (2.91)
8.disease2	10.64* (2.31)	1.827 (0.56)
nda_bla	0.0519** (-2.96)	0.115 (-1.85)
safety	1.167 (0.26)	0.0546*** (-3.45)
total_exp	2.043 (1.72)	1.789 (1.10)
total_rems	0.405 (-1.14)	0.0455** (-2.58)
N	110	110

Exponentiated coefficients; t statistics in parentheses

\* p<0.05, \*\* p<0.01, \*\*\* p<0.001

# Excluding PREA studies: N=75

	(1) safety_label	(2) efficacy_1~1
main		
total_pms	1.067 (0.26)	0.776 (-0.86)
required	12.81* (2.27)	4.673 (1.17)
1bn.design3	.	.
2.design3	0.0926 (-1.65)	0.169 (-1.55)
3.design3	0.0149 (-1.88)	0.152 (-0.83)
4.design3	0.119* (-2.16)	0.0344* (-2.29)
1bn.disease2	.	.
2.disease2	0.663 (-0.28)	4.007 (0.84)
3.disease2	248.7* (2.28)	142.1 (1.76)
5.disease2	2.279 (0.55)	0.975 (-0.01)
6.disease2	0.620 (-0.30)	46.55 (1.75)
7.disease2	6.849 (1.09)	558.4* (2.35)
8.disease2	5.474 (1.00)	7.026 (0.96)
nda_bla	0.0107** (-2.71)	0.00916* (-2.25)
safety	4.018 (1.27)	0.101 (-1.67)
total_exp	1.301 (0.38)	5.579 (1.49)
total_rems	0.0848 (-1.77)	0.211 (-0.99)
N	75	75

Exponentiated coefficients; t statistics in parentheses  
 \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

### Predicted probabilities, by requirement and design

	Safety label change			Efficacy label change		
	Required	Non-required	Difference	Required	Non-required	Difference
RCT	0.876	0.355	0.521	0.675	0.308	0.367
Non-R CT*	0.395	0.048	0.347	0.260	0.070	0.190
Observational	0.095	0.008	0.087	0.241	0.064	0.177
Nonclinical	0.456	0.062	0.394	0.067	0.015	0.052

#### Notes:

1. Other covariates held at their mean values. There are only 2 observations in observational study category.  
This is the predicted probabilities in the logit model.
2. \*: it includes 21 non-R trials and 10 trials (randomization unspecified)
3. N=75, without PREA studies

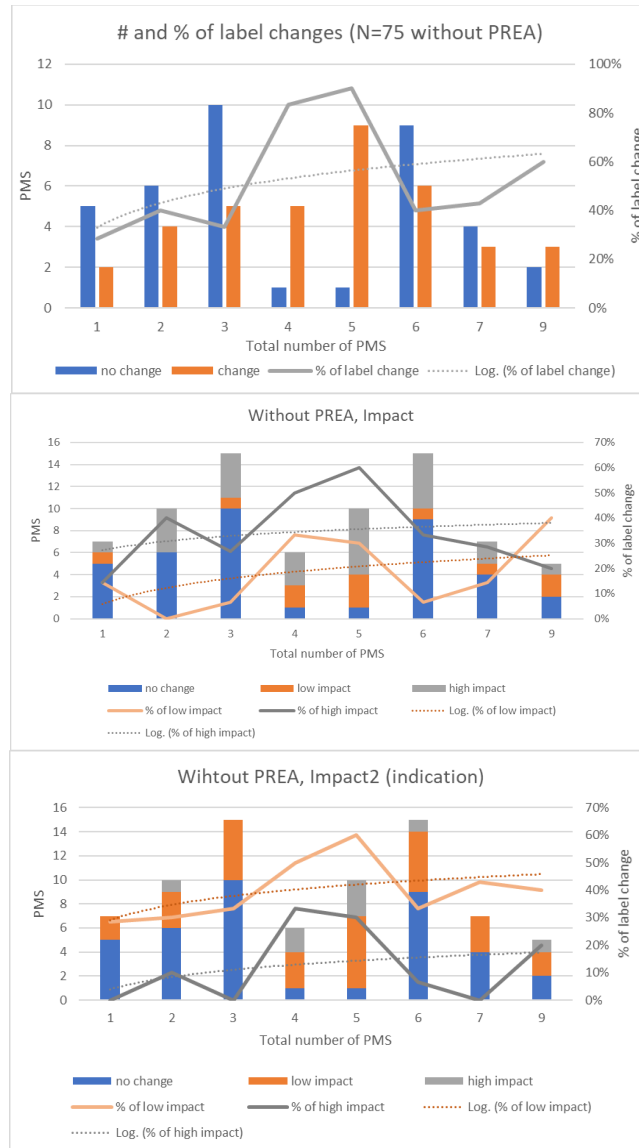
## **Appendix E for paper 2: Figures**

See Figure 4 (Contributions of Postmarketing Studies to Sponsors' Knowledge Base) in Tufts CSDD (2007) Impact Report. Volume 9, Number 3 • May/June 2007

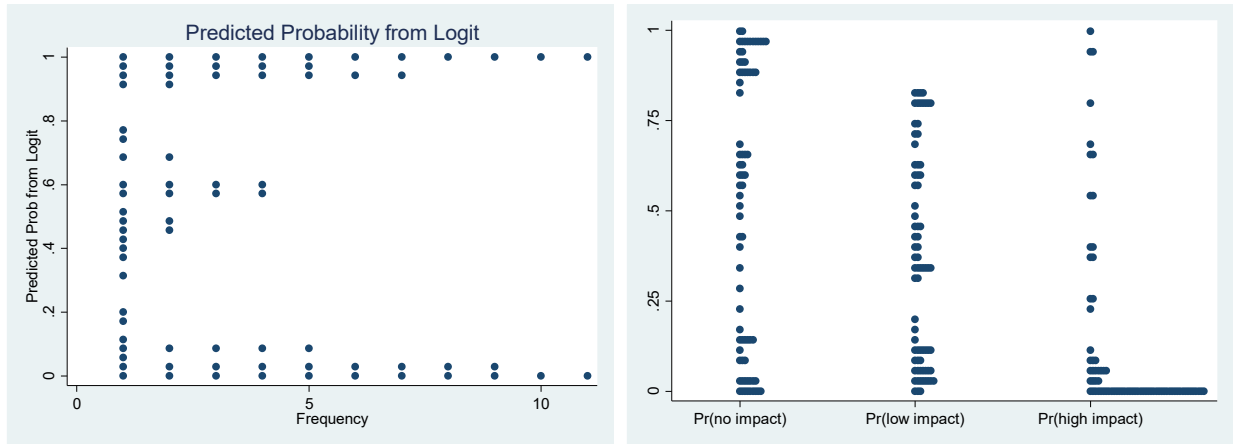
**Figure E-5. Contributions of Postmarketing Studies to Sponsors' knowledge base**

See Figure 1 in Lester, J., Neyarapally, G. A., Lipowski, E., Graham, C. F., Hall, M., & Dal Pan, G. (2013). Evaluation of FDA safety-related drug label changes in 2010. *Pharmacoepidemiology and drug safety*, 22(3), 302-305.

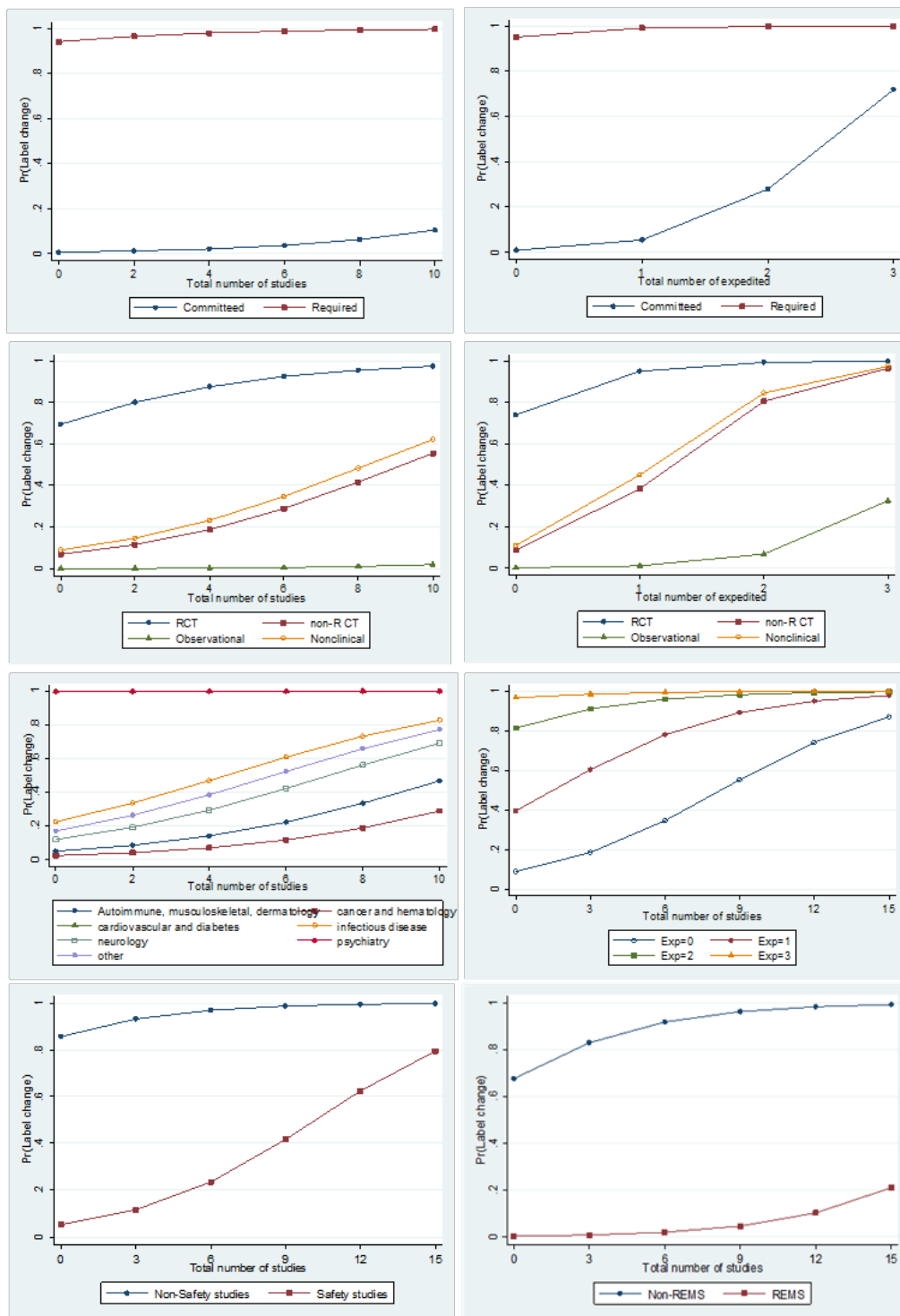
**Figure E-6. Label change initiator in 2010**



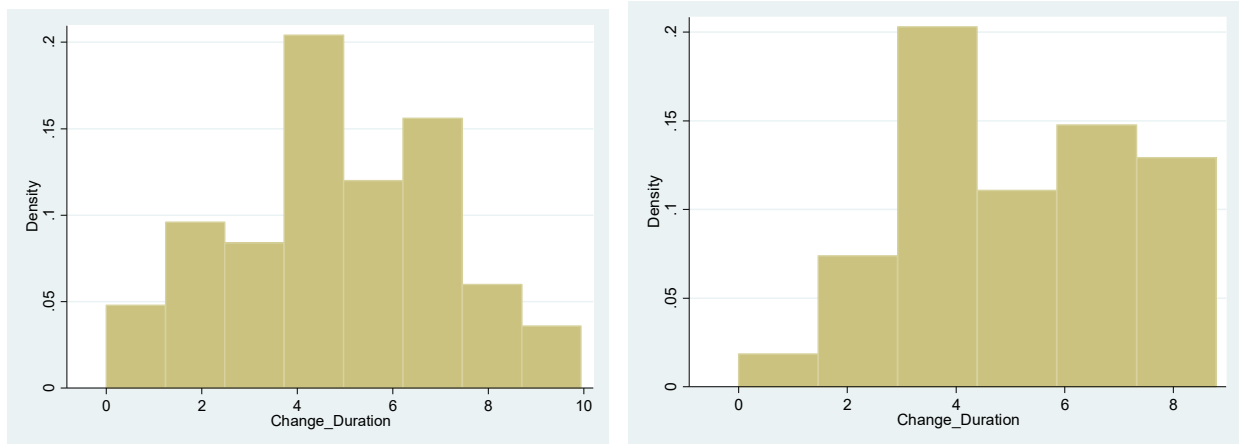
**Figure E-7. The total number of postmarketing studies and label changes**



**Figure E-8. Predicted probabilities of label change (Logit on left, Ologit on right)**



**Figure E-9. Predicted probabilities of label change by the number of postmarketing studies and Expedited approval paths**



**Figure E-10. Distribution for duration (label change date – PMR/PMC est. date) Left: including PREA, Right: excluding PREA**

See Exhibit 12 in Booz Allen Hamilton study (2008): postmarketing commitments study final report (January 2008), Independent Evaluation of FDA’s Prescription Drug User Fee Act III – Evaluations & Initiatives. Contract No. 223-04-8100 Task No. 4

**Figure E-11. Influence of product review factors on PMC decision (2008 BAH study), 2004-2007**

See Exhibit 24 in Booz Allen Hamilton study (2008): postmarketing commitments study final report (January 2008), Independent Evaluation of FDA’s Prescription Drug User Fee Act III – Evaluations & Initiatives. Contract No. 223-04-8100 Task No. 4

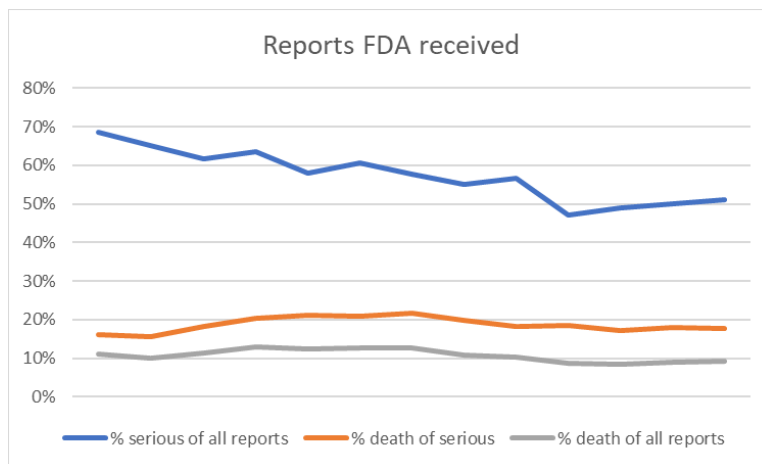
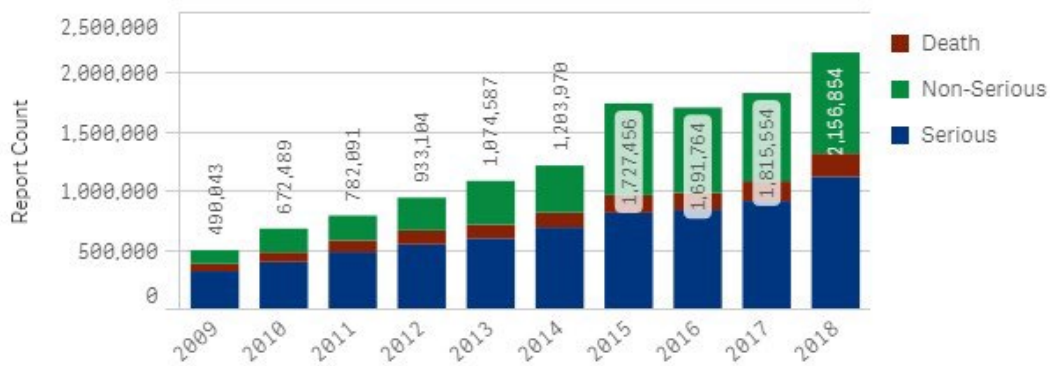
**Figure E-12. Fulfilled PMCs impact on Label changes (2008 BAH study), 2004-2007**

See Exhibit 5 in Booz Allen Hamilton study (2010): CDER Analysis, Evaluation and Technical Assistance, Contract Number GS-23F-9755H; Order Number: HHSF223200830363G, Deliverable 6: Final Report on the PMR/PMC Backlog Review

**Figure E-13. PMR/PMC Backlog by Year Established (BAH study, 2010), 2004-2007**



**Reports received by Report Seriousness**



**Figure E-14. Spontaneous reports FDA received over time**

[source: FDA Adverse Event Reporting System (FAERS) Dashboard]

Note: “Serious” indicates that one or more of the following outcomes, excluding death, were documented in the report: hospitalization, life-threatening, disability, congenital anomaly, required intervention, and/or other serious outcome. “Death” indicates that the outcome was documented as Death. “Non-Serious” is used for outcomes which were not documented as Serious or Death.

## Appendix F for paper 2: Descriptive analyses of PMR/PMCs and label changes

Table 2-28 presents an overview of PMR/PMCs and important label changes in the sample, excluding changes in sections 12-14 in drug labels. Among 110 PMR/PMCs, 67 studies resulted in important label changes (61%). But, this includes PREA studies that, FDA says, are fulfilled when labeling revision supplements are accompanied. When excluding PREA studies, 49% led to label changes. Required studies are more likely to make label changes compared to commitments. All accelerated approval requirements (AA studies) are updated in drug labels (100%). FDAAA safety studies have lower rate of label updates (53%) compared to AA studies, but still higher than commitments (41%).

**Table F-28. Label changes by postmarketing statutes**

Type of PM studies		Label change	No label change	Total
Requirements (PMR)	AA	4 (100%)	0	4
	PREA	30 (86%)	5	35
	FDAAA	17 (53%)	15	32
	PMR Total	51 (72%)	20	71
	PMR Total without PREA (AA+FDAAA)	21 (58%)	15	36
Commitments (PMC)		16 (41%)	23	39
TOTAL with PREA		67 (61%)	43	110
TOTAL without PREA		37 (49%)	38	75

Table 2-29 displays how many PMR/PMCs resulted in label changes by the following criteria: new vs. supplemental approval, NDA vs. BLA, REMS requirement, expedited approval paths, and orphan designation. We see that there is significant difference in the percentage of studies with label updates between NDAs and BLAs. Only 40% of PMR/PMCs with NDAs resulted in label changes compared to 87% for BLAs. It is notable that PMR/PMCs with BLAs are

much more likely to be required (67%) compared to NDAs (43%). Also, PMS with BLAs are more likely to be clinical trials (80%) compared to NDAs (55%). Also, new drug approvals have lower rate of label changes (44%) compared to supplemental approvals (67%). Although this is somewhat surprising, PMR/PMCs with supplemental approvals are more likely to be BLAs (50%) compared to new approvals (11%) and more likely to be clinical trials (72%) compared to new approvals (56%). Study design, whether or not a postmarketing study is required, and unidentified distinctive characteristics of biologics perhaps capture the differences.

**Table F-29. PMR/PMCs and label changes by approval paths and REMS, excl. PREA**

Without PREA	Label change	No label change	Total
New	25 (44%)	32	57
Supplemental	12 (67%)	6	18
NDA	24 (40%)	36	60
BLA	13 (87%)	2	15
NMEs	21 (54%)	18	39
Non-NMEs	16 (44%)	20	36
Expedited <sup>1</sup>	13 (48%)	14	27
PMS for AA approvals <sup>2</sup>	8 (80%)	2	10
Priority review <sup>3</sup>	13 (48%)	14	27
Fast track	3 (60%)	2	5
Traditional	24 (50%)	24	48
Orphan	8 (80%)	10	18
Non-orphan	29 (51%)	28	57
REMS	9 (38%)	15	24
No REMS	28 (55%)	23	51

Notes:

1. Expedited includes accelerated approval (AA), Fast track (FT), and Priority designations. Multiple designations can be allocated to a drug. All AA and FT drugs had priority review designation.
2. Here, the number of PMR/PMCs with accelerated approvals are PMR/PMCs that are associated with accelerated approvals in 2008. This number is different from the number of accelerated approval requirements because an accelerated approval has multiple PMR/PMCs and not all are accelerated approval requirements.
3. Priority review dominates expedited approval which means 100% of AA or FT expedited drugs had priority review designation as well.

From Table 2-29, as we expected, we find that PMR/PMCs for the drugs approved with AA path are much more likely to result in label changes (80%) compared to other drugs. Note that all AA requirements had labeling revisions. Also, fast track drugs' postmarketing studies have

higher rate of label change although the sample size is small. Combining AA and FT drugs, 73% of the PMR/PMCs associated with AA and/or FT approvals resulted in labeling revision. This is higher compared to traditional approvals (50%).

NMEs are more likely to have label changes based on PMR/PMCs (54%) than non-NMEs (44%). And, PMS with orphan drugs are more likely to result in labeling revision (80%) compared to PMS with non-orphan drugs (51%). And, drugs without REMS requirement had higher rate of labeling revision (55%) than those approvals with REMS requirement (38%).

Table 2-30 shows that the probability of a postmarketing study resulting in a label change can vary, depending on the purpose of the study (safety) and whether the study was required or committed. In total, as we supposed, safety studies are little more likely to result in label changes (51%) compared to non-safety studies (46%). The different is not significant. Of all commitments, safety studies have more label changes (44%) compared to non-safety studies (38%). Again, the different doesn't seem significant. When comparing safety requirements with safety commitments, slightly larger difference is observed (53% for FDAAA safety requirements and 44% for safety commitments). Within safety studies, the legal binding force that PMRs carry seems to be working to some extent.

**Table F-30. PMR/PMCs and Label changes by study purpose, excluding PREA**

Postmarketing studies		Label change	No label change	Total
FDAAA vs. PMC	FDAAA safety studies	17 (53%)	15	32
	PMC safety studies	8 (44%)	9	18
	PMC non-safety studies	8 (38%)	14	21
All PMR/PMCs excluding PREA	Safety studies	25 (51%)	24	49
	Non-safety studies	12 (46%)	14	26

Table 2-31 tells us how the likelihood of label changes varies by study design (data type). More labels were updated from the postmarketing studies where data source is high quality. It is not surprising that data from clinical trials are more likely to result in label changes compared to data from observational studies. Nonclinical studies include nonclinical toxicology studies, in vitro studies, and production/manufacturing related studies. Although these provide useful information, they are less likely to result in label changes in important sections (sections 1-8).

When looking at the number of label changes in prescribing information (excluding 12-14 sections), there is a clear contrast among study designs: 79% of randomized trials, 50% of non-randomized trials, 50% of observational studies, and only 20% of nonclinical studies resulted in label changes. Also, randomized trials are much more likely to change labels in important sections compared to any other designs.

**Table F-31. Label change by Data Source (study design), excluding PREA**

design	High impact (a)	Low impact (b)	Label change (c)	No change (d)	Total (c)+(d)
RCT	19	4	23 (79%)	6	29
Non-R CT	5	2	7 (50%)	7	14
Observational	1	0	1 (50%)	1	2
Nonclinical	1	5	6 (20%)	24	30
Total	26	11	37	38	75

Notes:

1. Label change (c) means any changes in label sections (excluding sections 12-14): BBW, indication, dosage, contraindication, warnings, adverse reactions, drug interactions, and subpopulation.
2. (a) high impact includes BBW, indication, dosage, contraindication, and warnings.

## **Appendix G for paper 2: Label change determination**

### **G.1 Work process**

Work scope:

All PMR/PMCs that are associated with new or supplemental NDA/BLAs that were approved in 2008. For sampling, supplemental approvals include SE1-SE8 codes and S codes only. I excluded other manufacturing control and labeling revision supplemental approvals in sampling approvals. I coded label updates twice and the last update was April 2018. This sample includes “fulfilled” or “submitted” PMR/PMCs.

Work process:

1. All approved labels and approval letters since 2008 were searched with NDA/BLA numbers.
2. A PMR/PMC description is compared to letters and changes in labels. All available labels and letters were searched to find the date of the label change that resulted from a PMR/PMC.
3. If I don't find the source of evidence in the approval letters, I go to Medwatch and search the label change to see if further data is available
  - a. I also google to see if any other data source is available
4. FDA safety communications (2010-2018) were searched
5. To double check, all BBWs were reviewed
  - a. Extracted all BBWs 2009-2017 from SLC/Medwatch
  - b. Compared NDA/drug brand names
  - c. Determined if the BBWs were based on PMR/PMCs established in 2008

6. To double check, all postmarketing drug safety evaluation summaries were reviewed (<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm>) for new NDA/BLAs that were approved in 2008<sup>155</sup>

Databases:

1. Drugs@FDA data <https://www.accessdata.fda.gov/scripts/cder/daf/>
2. FDA drug safety labeling change, MedWatch  
Since 1/1/2016: <https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/1/1/2008-6/30/2016>: <http://wayback.archive-it.org/7993/20170110235327/http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm>
3. FDA postmarketing drug safety evaluation  
<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm204091.htm#End>
4. FDA drug safety communication  
<https://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>
5. Clinicaltrials.gov: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
6. EMA clinical trial registry: <https://www.clinicaltrialsregister.eu/ctr-search/search>

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<sup>155</sup> Evaluated between 2008 and 2014 -- FDA is posting this information in accordance with section 505(r) of the FDCA. These postmarket evaluations are performed 18 months after approval of the drug or after its use by 10,000 individuals, whichever is later. Beginning not later than 18 months after approval, scientists from OSE/OND at CDER jointly review the relevant data.

## G.2 Justification

### NDA 22187 INTELENCE (ETRAVIRINE)

(NO CHANGE) NDA 22187-1 Study #1 PMC

Complete ongoing carcinogenicity study in mice and submit the final report.

11/24/2009 22187-s2 (no letter available)

\*\*\* Only section 13 (NONCLINICAL TOXICOLOGY -- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility) was changed.

(NO CHANGE) NDA 22187-1 Study #2 PMC

Complete ongoing carcinogenicity study in rats and submit the final report.

11/24/2009 22187-s2 (no letter available)

\*\*\* Only section 13 (NONCLINICAL TOXICOLOGY -- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility) was changed.

(changed) NDA 22187-1 Study # PREA fulfilled 3/27/2013

03/26/2012, S-009 Letter available, but no mention about PREA study

Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 6 years to 18 years of age. Conduct a pediatric safety and activity study of etravirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

03/26/2012 (letter available, but study not mentioned)

In the letter: This prior approval supplemental new drug application provides for a scored 25 mg tablet and expands the indication to include the treatment of HIV-1 infection, in treatment-experienced pediatric patients 6 years to less than 18 years of age in combination with other antiretroviral agents.

-----INDICATIONS AND USAGE----- INTELENCE is a human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for treatment of HIV-1 infection in treatment-experienced patients 6 years of age and older with viral strains resistant to an NNRTI and other antiretroviral agents. (1) In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE in combination with only N[t]RTIs. (1) Treatment history and resistance testing should guide the use of INTELENCE®. (1)

-----DOSAGE AND ADMINISTRATION----- • Adult patients: 200 mg (one 200 mg tablet or two 100 mg tablets) taken twice daily following a meal. (2.1, 2.3) • Pediatric patients (6 years to less than 18 years of age and weighing at least 16 kg): dosage of INTELENCE is based on body weight and should not exceed the recommended adult dose. (2.2, 2.3) • INTELENCE tablets should be taken following a meal. (2.2, 2.3)

-----ADVERSE REACTIONS----- The most common adverse drug reactions of moderate to severe intensity (at least 2%) which occurred at a higher rate than placebo in adults are rash and peripheral neuropathy. (6.1) The most common adverse drug reactions in at least 2% of pediatric patients are rash and diarrhea. (6.2)

#### 8.4 Pediatric use

Treatment with INTELENCE® is not recommended in children less than 6 years of age. The pharmacokinetics, safety, tolerability and efficacy of INTELENCE® in children less than 6 years of age have not been established [see Clinical Pharmacology (12.3)]. The safety, pharmacokinetic profile, and virologic and immunologic responses of INTELENCE® were evaluated in treatment-experienced HIV-1-infected pediatric subjects 6 years to less than 18 years of age and weighing at least 16 kg [see Adverse Reactions (6.2), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those



observed in adults, except for rash [see Adverse Reactions (6.2)]. Please see Dosage and Administration (2.2) for dosing recommendations for pediatric subjects 6 years to less than 18 years of age and weighing at least 16 kg.

\*\*\*\* This pediatric information was not available before. Although the letter doesn't mention the source of evidence, the data updated fits the specific description of this postmarketing study.

\*\*\* In FDA Postmarket Drug and Biologic Safety Evaluations (Sep 2007 – Dec 2009), serious AE reports on skin and hypersensitivity, liver, and coagulation problems were identified. FDA determined these events are adequately described in the current labeling as of December 2009.

(UNDETERMINED) NDA 22187/S-009 Study # PMC  
03/26/2012, Letter available, but no mention about PMC study

Conduct a study of etravirine in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.

### 12.3 Gender

No significant pharmacokinetic differences have been observed between males and females.

\*\*\* This 12.3 line was added, but I can't determine if this came from the PMS.

(changed) NDA 22187-1 Study #4 PMC  
Conduct an in vivo drug-drug interaction study between etravirine and buprenorphine/naloxone.  
10/07/2011, SUPPL-8 Letter available, but no mention about PMC study

7, 12. Narcotic ↔ etravirine INTELENCE® and buprenorphine (or buprenorphine/naloxone) can Analgesics/Treatment of ↓ buprenorphine be co-administered without dose adjustments, however, clinical Opioid Dependence: ↔ norbuprenorphine monitoring for withdrawal symptoms is recommended as buprenorphine, ↔ methadone buprenorphine (or buprenorphine/naloxone) maintenance therapy buprenorphine/naloxone\*, may need to be adjusted in some patients. methadone\* INTELENCE® and methadone can be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.

\*\*\* Such information on etravirine and buprenorphine was not available before.

(changed) NDA 22187-1 Study #5 PMC  
Conduct an in vivo drug-drug interaction study between etravirine and fluconazole.  
10/07/2011, SUPPL-8 Letter available, but no mention about PMC study

7, 12. Antifungals: ↑ etravirine Co-administration of etravirine and fluconazole significantly fluconazole\*, ↔ fluconazole increased etravirine exposures. The amount of safety data at these voriconazole\* ↑ voriconazole increased etravirine exposures is limited, therefore, etravirine and fluconazole should be co-administered with caution. No dose adjustment of INTELENCE® or fluconazole is needed. Co-administration of etravirine and voriconazole significantly increased etravirine exposures. The amount of safety data at these increased etravirine exposures is limited, therefore, etravirine and voriconazole should be co-administered with caution. No dose adjustment of INTELENCE® or voriconazole is needed.

\*\*\* Such information on etravirine and buprenorphine was not available before.

(changed) NDA 22187-1 Study #2 PMC  
Submit study reports for Week 48 data analyses for the ongoing Phase 3 studies TMC125-C206 and TMC125-C216 to support the traditional approval of etravirine.  
11/24/2009 22187-s2 (no letter available, but this is accelerated approval)

## 1 INDICATIONS AND USAGE

INTELENCE®, in combination with other antiretroviral agents, is indicated for the treatment of human

immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents. This indication is based on Week 48 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE®. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults.

Before: This indication is based on Week 24 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE™. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults.

12 Table 4: Population Pharmacokinetic Estimates of Etravirine 200 mg b.i.d. in HIV-1-Infected Subjects (Integrated Data from Phase 3 Trials at Week 48)\* Parameter Etravirine 200 mg b.i.d. N = 575 AUC<sub>12h</sub> (ng•h/mL) Geometric Mean ± Standard Deviation 4522 ± 4710 Median (Range) 4380 (458 - 59084) C<sub>0h</sub> (ng/mL) Geometric Mean ± Standard Deviation 297 ± 391 Median (Range) 298 (2 - 4852)

\*\*\* Efficacy approval was done. And such information was updated based on week 48 data.

#### NDA 22249 TREANDA (BENDAMUSTINE HYDROCHLORIDE) 3/20/2008

(UNDETERMINED) NDA 22249-1, PMC #7

Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: [...] sodium chloride).

\*\*\* Not enough information on this study

(UNDETERMINED) NDA 22249-1, PMC #1

Cephalon commits to providing an updated study report of Protocol 02CLLIII titled "Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) BCLL Requiring Therapy" at data cut off date in May 2008. Response rate, progression-free survival, overall survival and safety updates will be provided in this study report.

\*\*\* Searched with "Chlorambucil" and "Binet" and no changes were found. But, more information was updated— not enough information to call whether the changes were based on this study.

(NO CHANGE) NDA 22249-1, PMC#6

Cephalon commits to conducting in vitro screens to determine if bendamustine is a p-glycoprotein substrate or inhibitor.

\*\*\* No changes on Drug interaction, Pharmacology section on p-glycoprotein.

\*\*\* Adverse event reports of pneumocystis pneumonia were identified. FDA is continuing to evaluate the reports of pneumocystis pneumonia to determine if regulatory action is required. → updated: 08/28/2013 label changes section 6 adding pneumocystis pneumonia as a postmarketing experience. It is unclear that these pneumonia reports were from the study PMC #1, therefore it remains "undetermined"

#### BLA 103792

(NO CHANGE) NDA 103792 S-5175, PMC

To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by 31 March, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31, 2014.

\*\*\* In 2015, 12.2 Pharmacodynamics Cardiac Electrophysiology section was changed. No other sections of the label were changed.

(changed) NDA 103792 S-5175. PMC

To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of trastuzumab treatment in Study BO16348 (HERA) in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

\*\* The letter says the sections of label were changed based on evidence from PMC1 and PMC2. I couldn't find the revised label, but the letter confirms it.

(changed) NDA 103792 S-5175. PMC

To provide updated safety information of the observation and 1-year trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

Letter on 6/30/2014

"The Prior Approval Supplemental (PAS) biologics application sBLA 103792/5313 provides for the 8-year median duration follow-up results from the planned full analysis of the efficacy and safety of 1-year and 2-year Herceptin® treatment (8 mg/kg i.v. loading dose, 6 mg/kg i.v. every three weeks) versus observation and as a comparison of 1-year versus 2-years of Herceptin® treatment in fulfillment of PMC 1 and PMC 2 associated with sBLA 103792/5175. This PAS also provides for label revisions with safety findings from Study BO16348 (HERA) and a recommendation to not extend adjuvant treatment beyond 1-year which was added to the Dosage and Administration Section with supporting information provided in the Warnings and Precautions and Adverse Reaction sections."

\*\*\* The letter says the sections of label were changed based on evidence from PMC1 and PMC2. I couldn't find the revised label, but the letter confirms it.

(changed) NDA 103792 S-5187. FDAAA

To perform a DDI study in metastatic cancer patients to evaluate the impact of Herceptin on Carboplatin pharmacokinetics and to evaluate the impact of Carboplatin on Herceptin pharmacokinetics. Herceptin concentrations in the DDI study will be compared to clinical pharmacokinetic data from clinical studies BO16348, BO15935, and WO16229.

On label 11/20/2013

Section 7. Drug Interaction

In other pharmacokinetic studies, where Herceptin was administered in combination with paclitaxel, docetaxel, carboplatin, or doxorubicin, Herceptin did not alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed.

\*\*\* The letter on 11/20/2013 confirmed the study was fulfilled, and DDI section was updated.

(UNDETERMINED) NDA 103792 S-5187. FDAAA

To provide an update of cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic cardiac event.

(UNDETERMINED) NDA 103792 S-5187. PMC

To provide an update of efficacy from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 10 years of follow-up, with an interim update of efficacy at 5-years of follow-up.

## 5 WARNINGS AND PRECAUTIONS (04/23/2015 label)

In Study 1, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of 163 myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 164 8.7 years in the AC-TH arm.....Approximately 24% of 173 the surviving patients had recovery to a normal LVEF (defined as  $\geq 50\%$ ) and no symptoms on 174 continuing medical management at the time of last follow-up.

\*\*\* It is more likely that this information was changed based on the FDAAA study or PMC, but I can't tell for sure because 8.7 years of follow-up is between 5-10 years. There was no letter mentioning it.

## BLA 125160

(changed) BLA 125160-1, Study #6 FDAAA, fulfilled on Q3 2012

A placebo-controlled trial designed to assess the effects of CIMZIA treatment on antibody responses to a B cell-mediated immunization, using pneumococcal vaccine immunization, and to a T cell-mediated immunization, using influenza vaccine, in patients with active rheumatoid arthritis. The study will measure both antibody titers and rates of clinical response in approximately 100 placebo- and 100 CIMZIA-treated patients who will be given polyvalent pneumococcal polysaccharide vaccine and influenza vaccine.

\*\* Letter confirmed this PMR is fulfilled on 4/17/2012. Label update on immunization section was updated accordingly.

(changed) BLA 125160-1, Study #3 FDAAA, fulfilled on Q2 2014

CDP870-033, an ongoing open-label trial to assess the long-term safety of CIMZIA in patients with Crohn's disease who have previously completed trials CDP870-031 or CDP870-032. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA-treated patients. Patient follow-up will be extended to seven years from the start of treatment.

In clinicaltrials.gov, this study ID is NCT00160524 and completed in August 2012. Results first posted in October 2013.

Label updates on 10/17/2013

Section 5.2 "Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP)

concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk of using a TNF blocker in combination with azathioprine or 6-MP should be carefully considered." → class wide warning on TNF blocker

Label updates on 10/17/2013 Section 5.4 5.4 Hypersensitivity Reactions

"The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed [see Adverse Reactions (6.1)]."

Letter on 10/19/2015

"This "Prior Approval" supplemental biologics application provides for incorporation of the longterm incidence rate of antibody formation into the package insert."

Label updates on 10/19/2015

## Section 6 Immunogenicity

“Patients with Crohn’s disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to CIMZIA, the overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; approximately 6% were neutralizing in vitro.....Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively). The following adverse events were reported in Crohn’s disease patients who were antibody-positive (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection. In two long-term (up to 7 years of exposure), open-label Crohn’s disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma.....”

\*\* Letter on 10/19/2015 doesn’t say it is from PMS but the contexts indicate these changes from studies #3, #4, and #5

(changed) BLA 125160-1, Study #4 FDAAA, fulfilled on Q2 2014

CDP870-034, an ongoing open-label trial to assess the long-term safety of re-exposure to CIMZIA after a variable interval in patients with Crohn's disease who were previously withdrawn from completed trials CDP870-031 or CDP870-032 due to an exacerbation of Crohn's disease. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA-treated patients. Patient follow-up will be extended to seven years from the start of treatment.

\*\* Letter on 10/19/2015 doesn’t say it is from PMS but the contexts indicate these changes from studies #3, #4, and #5

(UNDETERMINED) BLA 125160-1, Study #5 FDAAA, fulfilled Q1 2016

CDP870-088, an open-label trial to assess the long-term safety of CIMZIA in patients with Crohn's disease who have either completed trial CDP870-085 or were withdrawn from CDP870-085 due to an exacerbation of Crohn's disease. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA-treated patients. Patient follow-up will be extended to five years from the start of treatment.

Label change supplemental approval on 2/3/2016 added the risk of TB. But, there’s no indication of this change being based on the PMR.

\*\* No letter confirms the fulfillment of this study and label changes based on this study

\*\*\*\* Adverse event reports of medication errors involving preparation and administration of Cimzia in vial form were identified and reviewed. The Dosage and Administration section of the labeling for Cimzia was updated August 2012, to include additional instructions about its preparation and administration. This change is not related to this PMS.

## NDA 22198, Sancuso (Granisetron)

(NO CHANGE) NDA 22198-1, PMC #6, fulfilled 3/4/2011

A clinical pharmacokinetic study to assess granisetron exposure in elderly individuals (over 65) that includes an even age distribution across the geriatric population.

Label updates on 9/28/2015 – section 12

“Elderly

Following application of Sancuso patch in healthy subjects, mean AUC<sub>0-z</sub>, C<sub>max</sub>, and C<sub>avg</sub> were 17%, 15%, and 16% higher, respectively in male and female elderly subjects (≥ 65 years) compared to younger subjects (aged 18-45 years inclusive). These pharmacokinetic parameters were largely overlapped between the two age groups with high variability (CV: >50%). Following a single 40 mcg/kg intravenous dose of granisetron hydrochloride in elderly volunteers (mean age 71 years), lower clearance and longer half-life were observed compared to younger healthy volunteers.”

\*\* The letter doesn't mention it, and only section 12 was changed.

(NO CHANGE) NDA 22198-1, PMC #5, fulfilled 3/4/2011

A clinical pharmacokinetic study to assess granisetron exposure in human subjects with differing levels of body fat.

On 09/28/2015, section 12 was changed.

“Body Mass Index

In a clinical study designed to assess granisetron exposure from Sancuso in subjects with differing levels of body fat, using body mass index (BMI) as a surrogate measure for subcutaneous fat, no significant differences were seen in the plasma pharmacokinetics of Sancuso in male and female subjects with low BMI [ $<19.5$  kg/m<sup>2</sup> (males),  $<18.5$  kg/m<sup>2</sup> (females)] and high BMI (30.0 to 39.9 kg/m<sup>2</sup> inclusive) compared to a control group (BMI 20.0 to 24.9 kg/m<sup>2</sup> inclusive).”

This particular information was updated on 9/28/2015. The letter doesn't mention the source of evidence, but the label itself reveals the source is from “a clinical study designed to assess granisetron exposure from Sancuso in subjects with differing levels of body fat” which is exactly same as this PMC description.

(NO CHANGE) NDA 22198-1, FDAAA #3, fulfilled 12/1/2010

A single-site, randomized, cross-over, thorough QT study that evaluates placebo, active control, bolus infusion granisetron, and transdermal granisetron in healthy volunteers.

Label update letter on 9/23/2011

This “Prior Approval” supplemental new drug application provides for updates to section 12.2 Pharmacodynamics of the package insert label to include information from completed thorough QT study 392MD/39/C.

\*\* On letter 09/23/2011, only section 12 was changed.

(changed) NDA 22198-1, PMC #4, fulfilled 1/11/2012

An appropriate in vitro or clinical pharmacokinetic study to determine the impact of heat on the delivery of granisetron from the transdermal system.

Label update on 9/28/2015

Section 5.4 was added

5.4 External Heat Sources

A heat pad should not be applied over or in vicinity of Sancuso patch. Patients should avoid prolonged exposure to heat as plasma concentration continues increasing during the period of heat exposure [see Clinical Pharmacology (12.3)].

\*\* The letter on 9/28/2015 doesn't say the source, but the revised section 12 says the change was based on “a study designed to assess the effect of heat on the transdermal delivery of granisetron from Sancuso in healthy subjects” that matches this PMC description.

NDA 22253/22254, Two separate NDAs, Vimpat (Lacosamide)

(NO CHANGE) NDA 22253/22254-1, FDAAA #2, final report 4/13/2011, fulfilled in Q3 2014

A nonclinical study in rats to examine the effects of Vimpat (lacosamide) on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing central nervous system structure and function than were employed in the standard pre- and postnatal development study. You should consider the use of multiple daily dosing as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern.

\*\* No information on brain development during the prenatal and early postnatal periods has been changed on label.

(NO CHANGE) NDA 22253/22254-1, PMC #3 fulfilled 8/31/2012

In vitro data to determine which enzymes may be involved in the metabolism of Vimpat (lacosamide) in addition to CYP2C19.

Letter on 9/25/2013

“The “Prior Approval” supplemental new drug application provides for revised labeling to remove all references to collapsing response mediator protein-2 (CRMP-2) based on new in vitro pharmacology studies, as well as updating the Drug Interactions and Metabolism and Elimination sections based on a new lacosamide drug interaction study with midazolam and a new in vitro study on additional CYP450 enzymes involved in lacosamide metabolism.”

\*\* Section 12.3 pharmacokinetics was updated with enzymes data and it is more likely from this PMC, but no major section was updated.

\*\*\* Per FDA postmarketing drug safety evaluation between Jan 2011 and June 2011, adverse event reports of cardiac conduction and “rhythm problems” were identified. And, FDA is continuing to evaluate these issues to determine if the current labeling, which includes these events in the Warnings and Precautions section, is adequate. These rhythm problems are unrelated to nonclinical toxicology (FDAAA #2) and in vitro study (PMC #3), and thus it wouldn’t change my coding.

### NDA 21356, Viread (tenofovir disoproxil fumarate)

(changed) NDA 21356-25, PREA #1 fulfilled 8/16/2012

Deferred pediatric studies under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 12 to < 18 years of age.

Letter on 8/16/2012:

“These Prior Approval supplemental new drug applications propose to expand the indication to include the treatment of chronic hepatitis B in patients 12 to less than 18 years of age, weighing at least 35kg.....

We reference the deferral granted in the August 11, 2008 approval letter for NDA 21356 S-025: 283-1 Deferred pediatric study under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 12 to <18 years of age.

Protocol Submission: COMPLETED

Study Start Date: ONGOING

Final Report Submission: JANUARY 2013 (72 week data)

We conclude that with these supplemental NDAs, you have fulfilled the above pediatric study requirement for ages 12 to less than 18 years for this application.”

\*\* The letter on 8/16/2012 confirms that the label change was resulted from this PREA.

(UNDETERMINED) NDA 21356-25, PMC #5, fulfilled 8/10/2010

Determine the susceptibility to tenofovir in cell culture of HBV harboring individually the following substitutions of conserved amino acid residues among HBV isolates: rtH35P, rtY111C, rtH156R, and rtI233T. Also, evaluate the [...] polymorphisms. For any substitutions showing [...] fold shifts in susceptibility to tenofovir, determine the shifts in susceptibility to adefovir, entecavir, and lamivudine.

The following was changed (section 1) in 2010:

“This indication is based primarily on data from treatment of nucleoside-treatmentnaïve subjects and a smaller number of subjects who had previously received lamivudine or adefovir. Subjects were adults with HBeAg-positive and HBeAgnegative chronic hepatitis B with compensated liver disease [See Clinical Efficacy in Patients with Chronic Hepatitis B (14.2)].

The numbers of subjects in clinical trials who had lamivudine- or adefovirassociated substitutions at baseline were too small to reach conclusions of efficacy [See Microbiology (12.4), Clinical Efficacy in Patients with Chronic Hepatitis B (14.2)].”

\*\* No letter mentions this study as the source of change. Data in section 1 was changed, but I can't determine if that change was based on this PMC. Section 12 data were changed, but these were minor changes.

\*\*\* There was one paragraph "Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to VIREAD and OBR" in section 8. But this is more likely

(NO CHANGE) NDA 21356-25, PMC #6, fulfilled 10/6/2010

Evaluate the use of tenofovir (TFV) versus TDF in susceptibility assays using isolates representing the range of susceptibilities.

\*\* No major changes were observed.

(changed) NDA 21356-25, FDAAA #4 fulfilled 2/14/2013

Perform annual genotypic and phenotypic analyses of HBV DNA from subjects who experience virologic failure to long-term TDF therapy (serum HBV DNA levels  $\geq$  400 copies/mL) in ongoing clinical trials out to 240 weeks (Studies 0102 and 0103) and 168 weeks (Study 0106). Submit a virology study report and cumulative resistance dataset each year.

(Note: studies GS-US-174-0102, GS-US-174-0103, and GS-US-174-0106)

On letter 10/7/2009:

"This supplemental new drug application was submitted to update the package insert (PI) with 96 week data from Studies GS-US-174-0102 and GS-US-174-0103; and updated resistance data from Study GS-US-174-0106, and to include important information in the patient package insert (PPI)."

On letter 10/14/2010

"This "Prior Approval" supplemental new drug application provides for the following revisions to the Package Insert based upon 144-week efficacy, safety and resistance data from Studies GSUS-174-0102 and GS-US-174-0103 in adult patients with HBeAg+ and HBeAg- chronic hepatitis B:

1. CLINICAL PHARMACOLOGY, Microbiology section

- Updates Resistance section with 144-week data

2. CLINICAL STUDIES, Clinical Efficacy in Patients with Chronic Hepatitis B section

- Updated to include information on Treatment beyond 48 Weeks"

On letter 9/19/2011:

"This "Prior Approval" supplemental new drug application provides for revisions to the Adverse Reactions (6.1), Clinical Trials (14.2), and Microbiology (12.4) sections of the Package Insert based upon 192-week efficacy, safety and resistance data from clinical trials GSUS-174-0102 and GS-US-174-0103 in adult patients with HBeAg+ and HBeAg- chronic hepatitis B."

On letter 8/7/2012:

"These Prior Approval supplemental new drug applications propose to include 240-week efficacy, safety and resistance data from Studies GS-US-174-0102 and GS-US-174-0103 in HBeAg-negative and HBeAg-positive adult patients with chronic hepatitis B and compensated liver disease in the Package Insert."

On letter 5/29/2015:

"These "Prior Approval" supplemental new drug applications provide updates to the package insert (PI) that include 384-week efficacy, safety and resistance data from Studies GS-US-174-0102 and GS-US-174-0103 in HBeAg-positive and HBeAg-negative adult patients with chronic hepatitis B and compensated liver disease."

\*\* Data from studies 102, 103, and 106 were the source of label change over time.

NDA 21894, Xenazine (Tetrabenazine)

(NO CHANGE) NDA 21894-1, FDAAA #1 fulfilled 12/13/2011



Complete the ongoing 2-year carcinogenicity study in male rats to identify the unexpected serious risk of carcinogenicity.

7/6/2011 label: "Carcinogenesis

No increase in tumors was observed in p53+/- transgenic mice treated orally with tetrabenazine at doses of 0, 5, 15 and 30 mg/kg/day for 26 weeks. When compared to humans receiving a 50 mg dose of XENAZINE, mice dosed with a 30 mg/kg dose of tetrabenazine produce about one sixth the levels of 9-desmethyl-beta-DHTBZ, a major human metabolite. Therefore, this study may not have adequately characterized the potential of tetrabenazine to be carcinogenic in people."

\*\* On 7/6/2011 label, section 13 (nonclinical toxicology) was updated. This is not major update.

(NO CHANGE) NDA 21894-1, FDAAA #5, fulfilled 12/13/2011

"Conduct a neurotoxicity study of tetrabenazine using methodology and a multiple dose regimen similar to Satou T et al. Exp Toxicol Pathol 53(4):303-308, 2001. Consideration should be given to including a group in which tetrabenazine is administered i.p. as in Satou et al. (2001) in order to facilitate comparisons between studies. Ideally, tetrabenazine should be tested at several dose levels with the high dose being a maximum tolerated dose."

\*\* I couldn't find information on neurotoxicity in the current and previous labels.

(NO CHANGE) NDA 21894-1, FDAAA #3, fulfilled 12/13/2011

Conduct a nonclinical toxicity study of fertility and early embryonic development (to implantation) to identify the unexpected serious risk of adverse effects on reproduction.

On label 7/6/2011:

"Impairment of Fertility

Oral administration of tetrabenazine (doses of 5, 15, or 30 mg/kg/day) to female rats prior to and throughout mating, and continuing through day 7 of gestation resulted in disrupted estrous cyclicity at doses greater than 5 mg /kg/day (less than the MRHD on a mg/m2 basis).

No effects on mating and fertility indices or sperm parameters (motility, count, density) were observed when males were treated orally with tetrabenazine (doses of 5, 15 or 30 mg/kg/day; up to 3 times the MRHD on a mg/m2 basis) prior to and throughout mating with untreated females. Because rats dosed with tetrabenazine do not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately assessed the potential of XENAZINE to impair fertility in humans."

\*\* 7/6/2011 label updated fertility section, but it is minor change.

(NO CHANGE) NDA 21894-1, FDAAA #6, final report 4/30/2009

Conduct an in vitro metabolism study to characterize the potential serious safety risk of the inhibitory effect of tetrabenazine, alpha-HTBZ, and beta-HTBZ on CYP2B6.

5/4/2011 label:

"The results of in vitro studies do not suggest that tetrabenazine,  $\alpha$ -HTBZ, or  $\beta$ -HTBZ are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. In vitro studies suggest that neither tetrabenazine nor its  $\alpha$ - or  $\beta$ -HTBZ metabolites are likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19."

\*\* Label was updated, but this change in section 12 is considered a minor change.

(NO CHANGE) NDA 21894-1, FDAAA #4 fulfilled 12/13/2011

Submit in vivo metabolism data in the animal species used in the nonclinical studies of tetrabenazine, particularly the reproductive toxicology and the carcinogenicity studies.

On 7/6/2011 label, section 13 mutagenesis was updated:

“Tetrabenazine and metabolites  $\alpha$ -HTBZ and  $\beta$ -HTBZ were negative in the in vitro bacterial reverse mutation assay. Tetrabenazine was clastogenic in the in vitro chromosome aberration assay in Chinese hamster ovary cells in the presence of metabolic activation.  $\alpha$ -HTBZ and  $\beta$ -HTBZ were clastogenic in the in vitro chromosome aberration assay in Chinese hamster lung cells in the presence and absence of metabolic activation. In vivo micronucleus tests were conducted in male and female rats and male mice. Tetrabenazine was negative in male mice and rats but produced an equivocal response in female rats.

Because the bioactivation system used in the in vitro studies was hepatic S9 fraction prepared from rat, a species that, when dosed with tetrabenazine, does not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately assessed the potential of XENAZINE to be mutagenic in humans. Furthermore, since the mouse produces very low levels of this metabolite when dosed with tetrabenazine, the in vivo study may not have adequately assessed the potential of XENAZINE to be mutagenic in humans.

\*\* update in section 13 is not considered a major change.

### BLA 125118, Orencia (Abatacept)

(NO CHANGE) BLA 125118-45, PREA #1 fulfilled 10/20/2010

Submission of the final study report for juvenile animal study DN07013.

On 8/25/2009 label, the following appeared since 2007:

“A juvenile animal study was conducted in rats dosed with abatacept from 4 to 94 days of age in which an increase in the incidence of infections leading to death occurred at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed. In addition, inhibition of T-cell-dependent antibody responses (TDAR) was observed. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed.”

\*\* The 4/7/2008 label is not available...that’s when BLA 125118-45 was approved. But, EMA data ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR - Assessment Report - Variation/human/002098/WC500236305.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002098/WC500236305.pdf)) says this study was completed on 6/9/2008 and the final report was submitted to the FDA on 6/26/2008. It is likely that this update was based on PREA #1. But this is a minor change.

(NO CHANGE) BLA 125118-45, PREA #3, fulfilled 10/20/2010

Submission of the protocol and submission of the final study report for the follow up juvenile animal study assessing the mechanism of T-regulatory cell depletion (DS07166).

\*\* EMA data ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR - Assessment Report - Variation/human/002098/WC500236305.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002098/WC500236305.pdf)) says this study was completed on 3/4/2008. The final report was submitted to the FDA on 12/4/2008. Same as above: 8/25/2009 label did update T-regulatory cell reduction. This is a minor change.

(UNDETERMINED) BLA 125118-45, PREA #2, fulfilled 10/20/2010

Submission of the protocol and submission of the final study report for the follow up juvenile rat study assessing the effects of exposure at post-natal day 4 versus post-natal day 28 (DS07165).

Label 08/25/2009 – the following was added in section 8 subpopulation, after 2007

“....However, exposure to abatacept in the juvenile rat, which may be more representative of the fetal immune system state in the human, resulted in immune system abnormalities including inflammation of the thyroid and pancreas [see Nonclinical Toxicology (13.2)].....

Studies in juvenile rats exposed to ORENCIA prior to immune system maturity have shown immune system abnormalities including an increase in the incidence of infections leading to death as well as inflammation of the thyroid and pancreas [see Nonclinical Toxicology (13.2)].”

\*\* According to the EMA, study DS07165 was completed on 1/12/2009. The final report was submitted to the FDA on 1/28/2009. It is likely that this was updated based on this PREA #2, but it is uncertain. The label changed in August 2009 doesn’t contain specific animal toxicity study data (we know it is from a juvenile rat toxicity study but there’s no info regarding day 4 vs. day 28, etc.). Label or letter on 10/20/2010 is not available. I conclude this case as “undetermined”

\*\* Checked on MedWatch database and it only contains information on adverse reaction change (section 6) regarding Clinical Experience in MTX-Naïve Patients and CLINICAL STUDIES: Adult Rheumatoid Arthritis which is irrelevant.

## NDA 21976, Prezista (Darunavir Ethanolate) approved 10/21/2008

(changed) NDA 21976-6, PREA #1 fulfilled 2/14/2012 final report 4/6/2011

Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients 3 to 6 years of age. Please evaluate dose requirements and safety in treatment-experienced pediatric patients 3 to 6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year olds in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

2/1/2013 letter:

“These “Prior Approval” supplemental new drug applications propose to update labeling with once daily dosing in:

- o HIV-1 infected, treatment-naïve pediatric patients 3 to less than 12 years of age, and
- o HIV-1 infected, treatment-experienced pediatric patients 3 to less than 18 years of age with no darunavir resistance associated substitutions.

These changes are based on pharmacokinetic modeling and simulation data that includes the darunavir/ritonavir pediatric clinical trials TMC114-C230, TMC114-C212, and TMC114-228.”

On 12/16/2011 letter:

“We note that you have fulfilled the pediatric study requirement for ages 3 to 6 years for this application.”

On 12/16/2011 label:

“indication

PREZISTA, co-administered with ritonavir (PREZISTA/ritonavir), and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in pediatric patients 3 years of age and older [see Use in Specific Populations (8.4)].

This indication is based on 24-week analyses of plasma HIV-1 RNA levels and CD4+ cell counts from 2 open-label Phase 2 trials in antiretroviral treatment-experienced pediatric patients (one trial in patients 6 to less than 18 years of age and one trial in patients 3 to less than 6 years of age).”

--- other sections are also changed: sections 1, 2, 8

\*\* The letter doesn't mention that the information was based on this PREA, but TMC114-228 is the study. Also, specific information relevant to this study was changed including population (age) and dosage for pediatric patients. PREA is fulfilled when a supplemental or new NDA is accompanied with the final report.

(UNDETERMINED) NDA 21976-6, PREA #2 fulfilled 2/14/2012 final report 4/12/2011

Perform a nonclinical reproductive toxicology study in a relevant species which achieves an adequate AUC exposure margin (compared to human serum exposure) in order to establish the safety profile of darunavir in utero. Submit your protocol for review prior to initiation of the reproductive toxicology study.

On 10/21/2008 label:

“In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.”

On 6/17/2016 label:

“8.3 Females and Males of Reproductive Potential  
Contraception

Use of PREZISTA may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients using combined hormonal contraceptives or the progestin only pill to use an effective alternative contraceptive method or add a barrier method of contraception [see Drug Interactions (7.3)].”

\*\* Relevant information was already updated on the 10/21/2008 label. On the 6/17/2016 label, section 8.3 on reproductive potential has been added, and no further major changes were found. But I’m not sure if the change on section 8.3 was resulted from this PREA study.

(changed) NDA 21976-7, PREA #1 fulfilled 3/25/2013 final report 7/31/2012

Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 12 to <18 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

2/1/2013 letter:

“These “Prior Approval” supplemental new drug applications propose to update labeling with once daily dosing in HIV-1 infected, treatment-naïve pediatric patients 12 to less than 18 years of age. These changes are based on pharmacokinetic, safety, tolerability, and virologic response data from clinical study TMC114-C230, which evaluated PREZISTA/ritonavir once daily dosing.”

...also

“These “Prior Approval” supplemental new drug applications propose to update labeling with once daily dosing in:

- o HIV-1 infected, treatment-naïve pediatric patients 3 to less than 12 years of age, and
- o HIV-1 infected, treatment-experienced pediatric patients 3 to less than 18 years of age with no darunavir resistance associated substitutions.

These changes are based on pharmacokinetic modeling and simulation data that includes the darunavir/ritonavir pediatric clinical trials TMC114-C230, TMC114-C212, and TMC114-228.”

2/1/2013 label:

“Indication – section 1

The indication for treatment-experienced pediatric patients 3 to less than 18 years of age is based on 24-week analyses of plasma HIV-1 RNA levels and CD4+ cell counts from two open-label Phase 2 trials in antiretroviral treatment-experienced pediatric subjects. The indication for treatment-naïve pediatric patients or antiretroviral treatment-experienced patients with no darunavir resistance associated substitutions is based on one open-label Phase 2 trial of 48 weeks duration in antiretroviral treatment-naïve subjects 12 to less than 18 years of age and pharmacokinetic modeling and simulation for patients 3 to less than 12 years of age.”

--- section 1, 2, and 5 were changed.

\*\* The added information in sections 1 (indication) and 2 (dosage) fit the description of this PREA.

(changed) NDA 21976-7, PREA #2 fulfilled 3/25/2013 final report 8/3/2012

Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 3 to <12 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety over 48 weeks.

2/1/2013 letter:

“These “Prior Approval” supplemental new drug applications propose to update labeling with once daily dosing in:

- o HIV-1 infected, treatment-naïve pediatric patients 3 to less than 12 years of age, and
- o HIV-1 infected, treatment-experienced pediatric patients 3 to less than 18 years of age with no darunavir resistance associated substitutions.

These changes are based on pharmacokinetic modeling and simulation data that includes the darunavir/ritonavir pediatric clinical trials TMC114-C230, TMC114-C212, and TMC114-228.”

2/1/2013 label:

“Indication – section 1

The indication for treatment-experienced pediatric patients 3 to less than 18 years of age is based on 24-week analyses of plasma HIV-1 RNA levels and CD4+ cell counts from two open-label Phase 2 trials in antiretroviral treatment-experienced pediatric subjects. The indication for treatment-naïve pediatric patients or antiretroviral treatment-experienced patients with no darunavir resistance associated substitutions is based on one open-label Phase 2 trial of 48 weeks duration in antiretroviral treatment-naïve subjects 12 to less than 18 years of age and pharmacokinetic modeling and simulation for patients 3 to less than 12 years of age.”

--- section 1, 2, and 5 were changed.

\*\* The added information in sections 1 (indication) and 2 (dosage) fit the description of this PREA.

## NDA 21992, Pristiq (Desvenlafaxine Succinate) 2/29/2008

(changed) NDA 21992-1, PMC #3 fulfilled 2/14/2013

"Although your NDA for desvenlafaxine succinate demonstrates effectiveness of recommended doses (50-100 mg/day) as a treatment for Major Depressive Disorder over an interval of 8 weeks, it does not provide information about the duration and conditions of treatment with desvenlafaxine that are necessary to sustain its antidepressant effects over the full duration (likely 6 months to a year or longer) of an acute major depressive episode at these same recommended doses. While it is widely assumed that continued treatment of symptomatically remitted patients reduces their risk of relapse, which is why the proposed labeling for desvenlafaxine recommends that treatment be continued beyond 8 weeks,

we have no evidence that desvenlafaxine at these lower doses has efficacy after 8 weeks. Once you have established the lower end of the dose-response curve for efficacy, you have agreed to conduct and submit the results of a randomized withdrawal study to address longer-term efficacy for your drug at appropriate doses. If the lower dose study establishes that 50 mg/day is the lowest effective dose, this study will evaluate doses of 50 and 100 mg/day. You have agreed to submit the results of this trial no later than 3 years after the date of initiation, or approximately 5.5 years from the date of approval for this NDA."

2/14/2013 letter says:

“We have received your submission dated April 16, 2012, containing the final report for the following postmarketing requirement listed in the February 29, 2008 approval letter.

1229-3 Although your NDA for desvenlafaxine succinate demonstrates effectiveness of recommended doses (50-100 mg/day) as a treatment.....

We have reviewed your submission and conclude that the above requirement was fulfilled.

...

. S-033, dated April 16, 2012, received April 17, 2012, a “Prior Approval” supplemental new drug application that proposes to add data in support of a new indication in adults for desvenlafaxine SR for the maintenance treatment of Major Depressive Disorder (MDD) and

. S-036, dated November 12, 2012 and received November 13, 2012, a “Changes Being Affected” supplemental new drug application that provides safety data updates to Section 6 Adverse Reactions.”

2/14/2013 label changes:

“1 INDICATIONS AND USAGE

PRISTIQ, a serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) [see Clinical Studies (14) and Dosage and Administration (2.1)]. The efficacy of PRISTIQ has been established in four short-term (8-week, placebo-controlled studies) and two maintenance studies in adult outpatients who met DSM-IV criteria for major depressive disorder

.....

### 2.3 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Longer-term efficacy of PRISTIQ (50-400 mg) was established in two maintenance trials [see Clinical Studies (14)]. Patients should be periodically reassessed to determine the need for continued treatment.”

\*\* Information that this PMC provides was changed in sections 1 and 2.

(changed) NDA 21992-1, PREA #1 final report 4/6/2017

"Deferred Pediatric Studies Under PREA

You have agreed to conduct studies to assess the safety and effectiveness of desvenlafaxine succinate as a treatment for Major Depressive Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) will be equally represented in the samples, and there will be a reasonable distribution of both sexes in these age strata. You have agreed to submit the results of these studies no later than 4.5 years after the date of approval for this NDA."

Letter on 02/06/2018:

"This "Prior Approval" supplemental new drug application provides for pediatric data to fulfill the postmarketing study requirement (PMR 1229-1) imposed under the Pediatric Research Equity Act for the assessment of safety and efficacy in pediatric patients with Major Depressive Disorder.

.....

Your April 6, 2017, submission contains the final report for the following postmarketing requirement listed in our February 29, 2008, approval letter.

1229-1 You have agreed to conduct studies to assess the safety and effectiveness of desvenlafaxine succinate as a treatment for Major Depressive Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11 years) and adolescents (ages 12 to 17) will be equally represented in the samples, and there will be reasonable distribution of both sexes in these age strata.

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all your postmarketing requirements and postmarketing commitments acknowledged in our February 29, 2008, letter."

Label changes on 2/6/2018:

"Dosage and Administration (2.5) 2/2018

Warnings and Precautions (5.2, 5.4, 5.5, 5.7) 2/2018"

\*\* The letter says the label was updated based on data from this PREA.

(changed) NDA 21992-1, PMC #4 fulfilled Q1 2014

While it is clear that desvenlafaxine has a qualitatively negative effect on sexual function from the adverse events collected during your earlier trials, we do not have quantified sexual dysfunction data. You have agreed to assess sexual dysfunction in your planned lower dose study. If the lower dose study establishes that 50 mg/day is the lowest effective dose, you have agreed to conduct another acute, randomized controlled trial with placebo, 50, and 100 mg/day, and employ a validated and reliable outcome measure to assess for sexual dysfunction. This study could be conducted in parallel with the longer-term efficacy trial, and the results could be submitted approximately 5.5 years from the date of approval for this NDA.

12/10/2013 letter says:

"We have received your submission dated August 19, 2013, containing the final report for the following postmarketing commitment listed in the February 29, 2008 approval letter.

1229-4 While it is clear that desvenlafaxine has a qualitatively negative effect on sexual function.....

We have reviewed your submission and conclude that the above commitment was fulfilled."

Label was updated on 12/10/2013:

"section 6. Adverse reaction 6.1 clinical studies experience

The most commonly observed adverse reactions in PRISTIQ treated MDD patients in short term fixed-dose studies (incidence  $\geq$  5% and at least twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

\*\* Although the letter doesn't mention the source of evidence, section 6.1 was updated on very specific data this PMC has addressed—sexual dysfunction. I conclude that this PMS was the source.

(changed) NDA 21992-1, PMC #5 fulfilled 1/13/2011

Your combined fertility and embryo-fetal toxicity study in rats did not adequately assess desvenlafaxine's potential for embryo-fetal toxicity, including teratogenicity, due to decreased number of fetuses available for analysis at the high dose of 300 mg/kg. This appeared to result from effects of desvenlafaxine on fertility and pre-implantation loss and would not be factors if dosing were only done during the period of organogenesis. Consequently, you have agreed to conduct a standard embryo-fetal toxicity study in rats, and submit the results no later than 3 years after the date of the approval for this NDA.

2/14/2013 label was updated on 8.1 pregnancy:

“Animal data

When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 300 mg/kg/day and 75 mg/kg/day, respectively, no teratogenic effects were observed. These doses are 30 times a human dose of 100 mg/day (on a mg/m<sup>2</sup> basis) in rats and 15 times a human dose of 100 mg/day (on a mg/m<sup>2</sup> basis) in rabbits. However, fetal weights were decreased and skeletal ossification was delayed in rats in association with maternal toxicity at the highest dose, with a no-effect dose 10 times a human dose of 100 mg/day (on a mg/m<sup>2</sup> basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation at the highest dose of 300 mg/kg/day. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 10 times a human dose of 100 mg/day (on a mg/m<sup>2</sup> basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine succinate at a dose 30 times a human dose of 100 mg/day (on a mg/m<sup>2</sup> basis).”

\*\* Data was updated and this was a major change. Although the 2/14/2013 doesn't mention about the source of evidence and this particular change, it is very likely that this nonclinical toxicology data came from this PMS

(changed) NDA 21992-1, PMC #2 fulfilled Q4 2014

Your NDA for desvenlafaxine succinate (DVS) demonstrates the effectiveness of doses as low as 50 mg as a treatment for Major Depressive Disorder (MDD), however, the available data for effectiveness for this drug in MDD suggests a flat dose response curve for efficacy between 50 and 400 mg/day. On the other hand, there is a clear dose response for adverse events as the dose increases from 50 to 400 mg/day. Therefore, there is a need to better understand the lower end of the dose response curve to determine if efficacy might be achieved at doses even lower than 50 mg/day. You have agreed to conduct and submit the results of a randomized controlled study including placebo and DVS doses of 10, 25, and 50 mg/day as a Postmarketing commitment. This study will assess efficacy in this dose range and will also include a validated and reliable outcome measure to assess for sexual dysfunction. You have agreed to submit the results of this trial no later than 3 years after the date of the approval for this NDA.

8/20/2014 letter says:

“Your April 25, 2014 submission contains the final report for the following postmarketing commitment listed in the February 29, 2008 approval letter.

1229-2 Your NDA for desvenlafaxine succinate (DVS) demonstrates the effectiveness of doses as low as 50 mg as a treatment for Major Depressive Disorder (MDD), however.....

We have reviewed your submission and conclude that the above commitment was fulfilled.”

“We also refer you to our February 29, 2008 Approval letter in which you agreed to explore lower dose response for effectiveness of lower strengths as a postmarketing commitment. This supplemental new drug application provides for revisions to the labeling for Pristiq for the 25 mg lower dose strength.”

8/20/2014 label update:

“section 2 dosage:

## 2.1 GENERAL INSTRUCTION FOR USE

The recommended dose for PRISTIQ is 50 mg once daily, with or without food. The 50 mg dose is both a starting dose and the therapeutic dose. PRISTIQ should be taken at approximately the same time each day. Tablets must be

swallowed whole with fluid and not divided, crushed, chewed, or dissolved. In clinical studies, doses of 10 mg to 400 mg per day were studied. In clinical studies, doses of 50 mg to 400 mg per day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg per day and adverse reactions and discontinuations were more frequent at higher doses. The 25 mg per day dose is intended for a gradual reduction in dose when discontinuing treatment. When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms [see Dosage and Administration (2.4) and Warnings and Precautions (5.9)].”

\*\* Letter does imply that the label change was due to this PMC. Sections 2, 3, and 5 were updated with dose specific information.

## NDA 22291, Promacta (Eltrombopag Olamine) 11/20/2008

(changed) NDA 22291-1, AA #1 fulfilled 2/25/2011

To complete trial TRA102537 entitled, "A randomized, double blind, placebo-controlled Phase 3 study, to evaluate the efficacy, safety, and tolerability of eltrombopag, a thrombopoietin receptor agonist, administered for 6 months as oral tablets once daily in adult subjects with previously treated chronic idiopathic thrombocytopenic purpura (ITP)."

2/25/2011 letter says:

“This supplemental new drug application provides for conversion of accelerated approval to full approval status, revised labeling, and proposed modifications to the approved REMS.

.....

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills the requirements made under 21 CFR 314.510. PMR 1196-1. To complete trial TRA102537 entitled, "A randomized, double-blind, placebo controlled.... PMR 1196-2. To complete trial TRA108057 entitled, "An open-label repeat dosing study of...."

2/25/2011 label updates:

Section 2

“For patients of East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once every other day [see Clinical Pharmacology (12.3)].”

\*\* The 2/25/2011 letter grants full approval based on the two accelerated approval PMRs. I consider them “major change” resulted from PMR/PMCs. Also, section 2—race—has been updated on 2/24/2011. It is likely that this change came from TRA108057.

BBW on 10/12/2016:

“Boxed Warning

CHRONIC HEPATITIS C

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.”

\*\*\* It is unclear on what this BBW was based.

(changed) NDA 22291-1, AA #2 fulfilled 2/25/2011

To complete trial TRA108057 entitled, "An open-label repeat dosing study of eltrombopag olamine in adult subjects, with chronic idiopathic thrombocytopenic purpura (ITP)."

\*\* See above AA #1.

(changed) NDA 22291-1, FDAAA #5 fulfilled Q2 2015 – actual completion: July 2015

To conduct trial TRA105325 entitled, "EXTEND (Eltrombopag extended dosing study): an extension study of eltrombopag olamine in adults, with idiopathic thrombocytopenic purpura (ITP), previously enrolled in an eltrombopag study." The protocol for this trial was previously submitted to FDA and the study is currently active. The protocol will be modified to include performance of bone marrow examinations prior to the initiation of Promacta (eltrombopag) Tablets, following 12 months of Promacta (eltrombopag) Tablets therapy as well as following the completion of 24 months of Promacta (eltrombopag) Tablets therapy; enrollment will continue until these data are obtained from at least 150 patients. An interim report will contain, in addition to any other items, results of bone



marrow evaluations for patients who have completed bone marrow evaluations at baseline and following 12 months of Promacta (eltrombopag) Tablets therapy.

10/12/2016 label updates:

Section 5

“In the three controlled clinical trials in adults with chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg of PROMACTA daily and 8 (7%) placebo-group patients. In the extension trial, cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. In the two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.”

\*\* Although the letter doesn't confirm the source of evidence, “extension trial” was mentioned as evidence in label itself.

### NDA 21506 Mycamine (Micafungin Sodium) 1/22/2008

(changed) NDA 21506-8, PREA #2 fulfilled 7/9/2013

The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose 4.5 mg/kg/day micafungin in pediatric patients from greater than or equal to 4 months to < 2 years old. This proposed weight-based dosing regimen of micafungin is predicted to result in micafungin exposures in younger children similar to that observed in adults dosed at the approved micafungin dose of 150 mg/day.

The letter on 6/21/2013 says:

“This “Prior Approval” supplemental new drug application provides for the addition of information regarding dosing regimens for pediatric patients greater than or equal to 4 months of age to the labeling.

.....

We note that you have fulfilled the pediatric study requirement for ages four months to 16 years for this application.”

Label updates on 6/21/2013:

Section 1

“Mycamine® is indicated in adult and pediatric patients 4 months and older for:....”

\*\* On 6/21/2013, sections 1 and 2 (dosage) were changed for pediatric patients greater than or equal to 4 months old. The 6/21/2013 pharmacology review document (Reference ID: 3270375) shows that the FDA reviewed these four studies thoroughly to change the label.

★★ (NO CHANGE -- decided no action) NDA 21506-8, PREA #4 fulfilled 7/9/2013, final report 4/14/2009

The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose intravenous micafungin, 7 mg/kg/day in neonates and infants weighing greater than or equal to 1000 grams, and 10 mg/kg/day in neonates and infants weighing < 1000 grams, to establish the appropriate dose(s) of micafungin in this age group. This study must be performed and analyzed by the sponsor, and the results reviewed by the FDA prior to initiating Study 5 to ensure appropriate micafungin dose selection for that study.

6/21/2013 pharmacology review document (Reference ID: 3270375, <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM363606.pdf>):

“The fourth phase 1 PK and safety study (9463-CL-2104) included in this submission contains data in neonates and young infants < 4 months of age. Astellas is not seeking an indication for this age group.

....

Median micafungin exposure (AUC) was higher in infants weighing < 1000 grams who received 10 mg/kg per day compared with infants weighing ≥ 1000 grams who received 7 mg/kg per day (median values: 291 mcg-h/mL versus 258 mcg-h/mL, respectively). Median total body clearance adjusted for weight was 26.7% higher in infants weighing < 1000 grams who received 10 mg/kg per day than in infants weighing ≥ 1000 grams who received 7 mg/kg per day (0.57 versus 0.45 mL/min/kg, respectively). Plasma micafungin concentration time profiles were similar in the 2 dose groups, as were the median C<sub>max</sub> (23.3 mcg/mL for 7 mg/kg/day versus 24.9 mcg/mL for 10 mg/kg/day) and the median elimination half-life (11.30 h for 7 mg/kg/day versus 10.43 h for 10 mg/kg/day; calculated using 2 serial time points: 8–12 h and 20–24 h after infusion start).

....

Mean micafungin AUC<sub>tau</sub> and C<sub>max</sub> increased with increasing dose, with weight-normalized CL<sub>ss</sub> larger in younger patients. There is a tendency for micafungin clearance to be greater in older (heavier) patients, but changes in micafungin clearance with age appear to be substantially explained by changes in body weight.”

\*\* The 6/21/2013 approval letter and label don't include patients younger than 4 months old (neonates and infants). The pharmacology document reviewed this PMR and the sponsor and FDA decided not to seek this patient population further. It was a conscious decision made by the sponsor and FDA.

(changed) NDA 21506-8, PREA #3 fulfilled 7/9/2013

The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose micafungin, 1.0 mg/kg/day for body weight greater than or equal to 25 kg and 1.5 mg/kg/day for body weight < 25 kg in pediatric patients greater than or equal to 4 months to 16 years old. These proposed weight-based dosing regimens of micafungin for antifungal prophylaxis are predicted to result in micafungin exposures in children similar to that observed in adults dosed at the approved micafungin dose of 50 mg/day.

\*\* See comments on PREA #2.

(changed) NDA 21506-8, PREA #1 fulfilled 7/9/2013

The primary objective of this study will be to evaluate the pharmacokinetics and safety of repeated dose micafungin, 3.0 mg/kg/day for body weight greater than or equal to 25 kg and 4.5 mg/kg/day for body weight < 25 kg, in pediatric patients from 2 to 16 years old. These weight-based dosing regimens of micafungin are predicted to result in micafungin exposures in children similar to that observed in adults dosed at the approved micafungin dose of 150 mg/day.

\*\* See comments on PREA #2.

NDA 22311, Mozobil (Plerixafor) 12/15/2008

(NO CHANGE) NDA 22311-1, FDAAA #4 fulfilled 6/3/2009, final report 1/23/2009

Complete and submit the data and final report from the thorough QT/QTc trial.

On letter 6/14/2010:

“We remind you of your Postmarketing Requirements (PMRs) in your submission dated December 11, 2008, these PMRs remain open. The requirements are listed below.

2. To provide follow up safety and efficacy information for trial 3101- L TF for 5 years.....

3. To provide follow up safety and efficacy information for trial 3102- L TF for 5 years....

.....

We remind you of your Postmarketing Commitment (PMC) in your submission dated December 11, 2008, this PMC remains open. The commitment is listed below.

5. Design, conduct and submit a clinical trial to evaluate weight based and flat dosing....”

“This "Changes Being Effected" supplemental new drug application provides for revisions to the Effects on Electrocardiogram subsection to Section 12.2, as requested by the FDA on June 22,2009, and to the Pharmacodynamics subsection of the package insert.”

The label 6/14/2010 adds section 12.4:

“12.4 QT/QTc Prolongation

Mozobil in single doses up to 0.40 mg/kg. In a randomized, double-blind, crossover study, 48 healthy subjects were There is no indication of a QT/QTc prolonging effect of administered a single subcutaneous dose of Mozobil (0.24 mg/kg and 0.40 mg/kg) and placebo. Peak concentrations for 0.40 mg/kg Mozobil were approximately 1.8-fold higher than the peak concentrations following the 0.24 mg/kg single subcutaneous dose.”

\*\* 6/14/2010 letter and label says that the QT data was updated, but this is not considered a “major change.”

(Changed) NDA 22311-1, PMC #5 fulfilled Q1 2015, final report Q3 2014

Design, conduct and submit a clinical trial to evaluate weight based and flat dosing schedules in lower weight NHL patients. The applicant should conduct sparse PK sampling and measure CD34+ cell counts at time points similar to those in protocol AMD3100-3101.

Letter on 8/4/2015:

“This Prior Approval supplemental new drug application provides for revisions to the Mozobil United States Prescribing Information (USPI) and includes dosing changes that are reflected in Section 2 Dosage and Administration and Section 12 Clinical Pharmacology.”

8/4/2015 label updates on section 2:

“The recommended dose of Mozobil by subcutaneous injection is based on body weight:

- 20 mg fixed dose or 0.24 mg/kg of body weight for patients weighing  $\leq 83$  kg. [see Clinical Pharmacology (12.3)]
- 0.24 mg/kg of body weight for patients weighing  $>83$  kg.

Use the patient’s actual body weight to calculate the volume of Mozobil to be administered. Each vial delivers 1.2 mL of 20 mg/mL solution, and the volume to be administered to patients should be calculated from the following equation.....

.....

In patients with moderate and severe renal impairment (estimated creatinine clearance (CLCR)  $\leq 50$  mL/min), reduce the dose of Mozobil by one-third based on body weight category as shown in Table 1. If CLCR is  $\leq 50$  mL/min the dose should not exceed 27 mg/day, as the mg/kg-based dosage results in increased plerixafor exposure with increasing body weight. [see Clinical Pharmacology (12.3)] Similar systemic exposure is predicted if the dose is reduced by one-third in patients with moderate and severe renal impairment compared with subjects with normal renal function. [see Clinical Pharmacology (12.3)]”

\*\* Section 2 was updated on weight-based and fixed dosage for the patients with lower weight (83 kg as a threshold). Although the letter doesn’t specify the source of evidence, given that this PMR was fulfilled in the first quarter of 2015 and that the label update is relevant to information this PMR provides, I consider this label update a major change based on the results of this PMR.

(Changed) NDA 22311-1, FDAAA #1 fulfilled 4/16/2010, final report 6/30/2009

Screen plerixafor in vitro to assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an in vivo drug-drug interaction trial may be needed.

6/14/2010 label updates on section 7:

“7 DRUG INTERACTIONS

Based on in vitro data, plerixafor is not a substrate, inhibitor or inducer of human cytochrome P450 isozymes. Plerixafor is not likely to be implicated in in vivo drug-drug interactions involving cytochrome P450s. At concentrations similar to what are seen clinically, plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an in vitro study. [see Clinical Pharmacology (12.3)]”

\*\* See comments on FDAAA #4

\*\*\* Although the 6/14/2010 letter doesn’t mention the source of evidence, the changed label fits the description of this PMR and the data provided is very specific (P-glycoprotein).

(UNDETERMINED) NDA 22311-1, FDAAA #2 fulfilled Q3 2014, final report 10/5/2012

To provide follow up safety and efficacy information for trial 3101-LTF for 5 years which will include death and disease status (relapse or disease-free). Updated status reports to be submitted annually.

\*\* Sections 4, 5, and 6 were changed on 6/4/2013 – mainly safety information on Anaphylactic shock and Hypersensitivity reactions (contraindications, warnings and precautions sections). It is possible that this data came from this PMR, but I am not confident enough to say that this change is due to FDAAA #2. I conclude this is UNDETERMINED.

(UNDETERMINED) NDA 22311-1, FDAAA #3 fulfilled Q3 2014, final report 10/5/2012

To provide follow up safety and efficacy information for trial 3102-LTF for 5 years which will include death and disease status (relapse or disease-free). Updated status reports to be submitted annually.

\*\* See comments on FDAAA #2

#### BLA 125249, Arcalyst (Rilonacept) approved 2/27/2008

(UNDETERMINED) BLA 125249-0, PMC #5 fulfilled Q2 2011

To assess whether either lower maintenance doses or a longer interval between doses could be equally effective as, but potentially safer than, the approved dose. The study could be designed to randomize patients on rilonacept to blindly continue on the approved dose or to switch to a lower dose or a longer interval between doses and to assess symptom scores over, for example, 9 weeks.

\*\* Label is not available on the FDA website.

(UNDETERMINED) BLA 125249-0, PMC #4—disappeared in Q4 2010

To conduct a pharmacokinetics (PK) study in the pediatric population.

\*\* Label is not available on the FDA website. And, I am not sure if this PMC was fulfilled because it disappeared in the system in Q4 2010.

#### BLA 125085, Avastin (Bevacizumab) approved 2/22/2008

(Changed) BLA 125085-91, PMC #2 fulfilled Q1 2011

To submit a clinical study report, including summary analyses and primary datasets, for study AVF3693g, "A Phase 3, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer."

12/20/2011 letter says:

"This "Prior Approval" labeling supplement to your biologics license application proposes to revise the package insert to remove the metastatic breast cancer indication, to remove information based on the results of studies E2100 and AVF2119g from the DOSAGE AND ADMINISTRATION, CLINICAL STUDIES, and USE IN SPECIFIC POPULATIONS, Geriatric Use sections of labeling, and to remove subsections of the ADVERSE REACTIONS section limited to the description of adverse reactions in these studies."

Sections 1, 2, 6, and 8 were changed.

In 2008, Avastin was granted accelerated approval for treatment of advanced breast cancer by the FDA pending submission of supplementary satisfactory evidence. BO17708 (AVADO) and AVF3694g (RIBBON1) trials were required (AA #1) and AVF3693g (RIBBON2) trial was committed (PMC #1). In 2010, ODAC voted to withdraw this indication. On December 16, 2010, CDER issued Complete Response letters for the three sBLAs based on AVADO, RIBBON1 and RIBBON2, stating that the data did not demonstrate sufficient benefit to outweigh the risks. Additionally, due to CDER's determination that the subsequent studies, AVADO and RIBBON1, along with RIBBON2, did not confirm the magnitude of benefit from E2100, CDER communicated that it was proposing to withdraw marketing approval of the drug in breast cancer and issued a Notice of Opportunity for a Hearing. On 1/16/2011, Genentech requested an hearing and on 28–29 June 2011, FDA Oncologic Drugs Advisory Committee hearing recommended the indication withdrawal. In November 2011, FDA withdrew officially the indication.

\*\*\* Although the 12/20/2011 letter doesn't specify the three trials (AVADO, RIBBON1, and RIBBON2), the two postmarketing studies came with BLA 125085-91 were used to change indication.

BBW warning revision/added on 12/5/2017:

*"Boxed Warning*

*Additions and/or revisions underlined:*

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

*Gastrointestinal Perforations:* The incidence of gastrointestinal perforation, some fatal, in patients receiving Avastin ranges from 0.3% to 3%. Discontinue Avastin in patients who develop gastrointestinal perforation *Surgery and Wound Healing Complications:* The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in patients receiving Avastin. Discontinue Avastin in patients who develop wound healing complications that require medical intervention. Withhold Avastin at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery, and until the wound is fully healed.

*Hemorrhages:* Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occur up to 5-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with a recent history of hemoptysis. Discontinue in patients who develop Grade 3-4 hemorrhage."

\*\*\* This BBW was revised on 12/6/2017, but it is rather changes on wording and it is less likely that this change was based on PMR/PMCs on breast cancer.

(Changed) BLA 125085-91, AA #1 study completed on 2/4/2008

To submit an efficacy supplement containing the final study reports (including summary analyses and primary datasets) and revised labeling based on the results from both of the following studies:

Study BO17708, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel Plus Placebo as First-Line Treatment for Patients with HER2-Negative Metastatic Breast Cancer." The protocol and a revised statistical analysis plan were submitted to IND 7023 on January 8, 2008, and February 1, 2008, respectively. The study was completed on February 4, 2008.

Study AVF3694g "A Multicenter, Phase 3, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer." The protocol was submitted to IND 7023 on August 14, 2007. Patient accrual has been completed and the study will be completed by February 28, 2009. The supplement will be submitted by July 1, 2009. We expect you to complete reporting of these studies within the framework described in your letter of February 20, 2008, and summarized above.

\*\*\* See comments above for PMC #1.

NDA 22090, Eovist (Gadoxetate Disodium) approved 7/3/2008

(NO CHANGE) NDA 22090-1, PREA #1 fulfilled 3/27/2015

Deferred pediatric study under PREA for use in magnetic resonance imaging (MRI) of the liver in pediatric patients ages 0 to 2 months with known or suspected hepatobiliary pathology. This study will obtain evaluable safety and imaging data from at least 10 subjects, however, due to the anticipated rarity of these clinical conditions in this pediatric population, progress towards recruitment will be assessed at one year after study start and the targeted number of patients may require adjustment. Any adjustment in the sample size will be supplied in a protocol amendment that contains supportive information and a request for FDA concurrence. Descriptive statistics will summarize safety and efficacy outcomes. Efficacy determination will be based upon extrapolation from studies in other patient populations.

3/27/2015 letter:

"We reference your submission dated November 27, 2013, Final Report for PMR 1324-2 and your interim report/submission dated March 4, 2015, reporting on the following postmarketing requirement:  
1324-1 Deferred pediatric study under PREA for use in magnetic resonance imaging (MRI) of the liver in pediatric patients ages 0 to 2 months with known or.....

We note the FDA granted deferral extension of the Final Report Submission date to the following: New Final Report Submission: December, 2015

We have reviewed your submissions and conclude that the above requirement was fulfilled.

This completes all of your postmarketing requirements acknowledged in our July 3, 2008, letter."

\*\* Although the letter says this PREA was fulfilled, there was no label change on pediatric patients ages 0 to 2 months.

(changed) NDA 22090-1, PMC #4 fulfilled 7/26/2012

To conduct a single center crossover study to evaluate the possible influence of Erythromycin as an example of an inhibitor of the organic anion transporting peptide on the hepatocyte uptake of Eovist in liver MR imaging in healthy subjects.

11/16/2011 label updates section 7 drug interactions:

“7.1 Interference with OATP Inhibitors

An interaction study in healthy subjects demonstrated that the co-administration of the OATP inhibitor erythromycin did not influence efficacy and pharmacokinetics of EOVI<sup>ST</sup>. No further clinical interaction studies with other medicinal products have been performed.”

\*\* Although the 11/16/2011 doesn't mention about the source of evidence, the updated information fits the description of PMC #4 and is specific enough to assume that this information was updated based on PMC #4.

(changed) NDA 22090-1, PREA #2 fulfilled 11/25/2014

To conduct the study entitled, "An observational study of the administration of Eovist in pediatric patients who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions." This study will enroll subjects aged > 2 months to 18 years and obtain evaluable safety and imaging data from at least 50 subjects. Efficacy will be assessed based upon comparison of uncontrasted images to Eovist-contrasted images. Descriptive statistics will summarize safety and efficacy outcomes.

3/27/2015 letter says:

“This “Prior Approval” supplemental new drug application proposes to add the clinical findings from an observational study in pediatric age group greater than 2 months to 18 years in section 8.4 of the package insert in fulfillment of a PMR from July 2008 approval letter.

....

We note that you have fulfilled PMR 1324-2, the pediatric study requirement for ages greater than 2 months to 18 years, for this application as stated in FDA Fulfillment letter dated November 25, 2014.”

\*\* The letter implies that section 8 was updated based on this PREA.

NDA 22195, 22207 Morphine Sulfate 3/17/2008

(NO CHANGE) NDA 22195-1, 22207-1, PMC #2 fulfilled 1/6/2011

"A minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%:

- a. 10-hydroxymorphine
- b. pseudomorphine, and
- c. morphine-N-oxide"

\*\* No specific and relevant information was updated in labels. The 1/23/2012 label updates mutagenesis section “No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the in vivo mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the in vivo clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, in vitro studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.” But, it doesn't refer any original studies and even if it did, this is minor change (section 13).

Boxed Warning on 12/16/2016:

“WARNING: RISK OF MEDICATION ERRORS

(additions underlined) ADDICTION, ABUSE, AND MISUSE; LIFE- THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering Morphine Sulfate Oral Solution. Dosing errors due to confusion between mg and mL, and other morphine solutions of different concentrations can result in accidental overdose and death.

#### Addiction, Abuse, and Misuse

Morphine Sulfate Oral Solution exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Morphine Sulfate Oral Solution, and monitor all patients regularly for the development of these behaviors and conditions.

#### Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Sulfate Oral Solution. Monitor for respiratory depression, especially during initiation of Morphine Sulfate Oral Solution or following a dose increase.

#### Accidental Ingestion

Accidental ingestion of even one dose of Morphine Sulfate Oral Solution, especially by children, can result in a fatal overdose of morphine.

#### Neonatal Opioid Withdrawal Syndrome

Prolonged use of Morphine Sulfate Oral Solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

#### Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Morphine Sulfate Oral Solution and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation."

\*\*\* This BBW was a class action on opioid and this BBW doesn't contain information on genetic mutation/chromosome aberration.

#### BLA 125268, Nplate (Romiplostim) 8/22/2008

(NO CHANGE) BLA 125268-1, FDAAA #3 – status unknown. Disappeared since Q4 2013

"To conduct a milk only lactation study in the subset of women enrolled in the pregnancy registry that choose to breastfeed their infants. This study will be designed to detect the presence and concentration of romiplostim in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

You will conduct this study according to the following timetable:

Protocol Submission: November 2008; Study Start: May 2009; First interim report submission: May 2010 then annually; Final Report: Within six months of FDA notification that sufficient data has been collected."

\*\* It is unclear whether this FDAAA was fulfilled. But there's no information updated concerning FDAAA #3

(Changed) BLA 125268-1, FDAAA #1 fulfilled Q2 2016

"To conduct an ""Antibody Registry Study"" that will enroll subjects who have received romiplostim and whose blood samples contain antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack or loss of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers are to submit blood samples to Amgen for detection of antibodies to romiplostim and thrombopoietin. The Antibody

Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.

You will conduct this study according to the following timetable:

Protocol Submission: November 2008; Study Start: May 2009; First interim report submission: May 2010 then annually; Final Report Submission: Within six months of FDA notification that sufficient data has been collected"

4/19/2016 letter says:

"We have received your submission dated October 20, 21015, containing the final report for the following postmarketing requirement listed in the August 22, 2008 approval letter for BLA 125268.

PMR 2396-1 To conduct an "Antibody Registry Study"....."

4/19/2016 label updates section 6:

"In clinical studies in patients with ITP, the incidence of preexisting antibodies to romiplostim was 5% (53/1112) and the incidence of binding antibody development during treatment with Nplate or a non-US approved romiplostim product was 4% (50/1112). The incidence of preexisting antibodies to endogenous TPO was 4% (40/1112) and the incidence of binding antibody development to endogenous TPO during treatment was 3% (38/1112). Of the patients with positive binding antibodies that developed to romiplostim or to TPO, five patients had neutralizing activity to romiplostim and none had neutralizing activity to TPO. No apparent correlation was observed between antibody activity and clinical effectiveness or safety.

A post marketing registry study involving patients with thrombocytopenia on Nplate or a non-US approved romiplostim product was conducted to assess the long-term consequences of the anti-romiplostim antibodies. Patients who lacked response or lost response to Nplate or a non-US approved romiplostim product were enrolled. The incidence of new binding antibody development was 3% (5/186) to romiplostim and 1% (2/186) to TPO. One patient was positive for binding antibodies to both romiplostim and TPO. Of the five patients with positive binding antibodies to romiplostim, two (1%) were positive for neutralizing antibodies to romiplostim only."

\*\* Although the letter doesn't specify the source of evidence, the label was changed in the section and data this PMR aimed to bring. And, the letter acknowledges this PMR was fulfilled on the same date. I conclude this as a label change resulting from this PMR.

(changed) BLA 125268-1, FDAAA #4, fulfilled Q4 2015

"To conduct trial 20080009, ""A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)."" In this trial, at least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule will apply to the detection of antibody formation to romiplostim and thrombopoietin as well as the electrocardiographic (ECG) detection of cardiac conduction abnormalities. A first interim report will contain, in addition to any other items, ECG and the results of bone marrow evaluations for patients who have completed 12 months of trial participation. This information will be updated for patients who have completed 24 months of trial participation and submitted in a second interim report."

4/19/2016 label updates section 5:

*"Bone Marrow Reticulin Formation and Collagen Fibrosis*

Nplate administration may increase the risk for development or progression of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation of Nplate. In a clinical trial, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy.

An open-label clinical trial prospectively evaluated changes in bone marrow reticulin formation and collagen fibrosis in adult patients with ITP treated with Nplate or a non-US approved romiplostim product. Patients were administered romiplostim by SC injection once weekly for up to 3 years. Based on cohort assignment at time of study enrollment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort1), year 2 (cohort 2) or year 3 (cohort 3) in comparison to the baseline bone marrow at start of the trial. Patients were evaluated for bone marrow reticulin formation and collagen fibrosis using the modified Bauermeister grading scale. From the total of 169 patients enrolled in the 3 cohorts, 132 (78%) patients were evaluable for bone marrow collagen fibrosis, and 131 (78%) patients were



evaluable for bone marrow reticulin formation. Two percent (2/132) of patients (both from cohort 3) developed grade 4 findings (presence of collagen). There was no detectable bone marrow collagen in one patient on repeat testing 12 weeks after discontinuation of romiplostim. Progression of bone marrow reticulin formation (increase greater than or equal to 2 grades or more) or an increase to Grade 4 (presence of collagen) was reported in 7% (9/131) of patients.”

\*\* 4/19/2016 label mentions a study as the source of evidence and the description fits this PMR #4.

### NDA 21775, Entereg (Alvimopan)

(UNDETERMINED) NDA 21775-1, FDAAA #3 fulfilled 12/21/2012 final report 6/29/12

A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management or postoperative ileus in patients undergoing radical cystectomy.

Actual Primary Completion Date: January 2012 (clinicaltrials.gov)

Actual Study Completion Date: January 2012 (clinicaltrials.gov)

10/18/2013 letter says:

“We acknowledge that your submission dated December 21, 2012, includes the final report for the following postmarketing requirement listed in the May 20, 2008 approval.

918-3 A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the ....

We have reviewed your submission and conclude that the above requirement was fulfilled.”

10/18/2013 label updates:

. Black box warning

“WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE: FOR SHORT-TERM HOSPITAL USE ONLY

There was a greater incidence of myocardial infarction in alvimopan-treated patients compared to placebo-treated patients in a 12-month clinical trial, although a causal relationship has not been established. In short-term trials with ENTEREG®, no increased risk of myocardial infarction was observed [see Warnings and Precautions (5.1)].

Because of the potential risk of myocardial infarction with long-term use, ENTEREG is available only through a restricted program for short-term use (15 doses) under a Risk Evaluation and Mitigation Strategy (REMS) called the ENTEREG Access Support and Education (E.A.S.E.®) Program [see Warnings and Precautions (5.1) and (5.2)].”

Also, sections 1 and 5 were updated on 10/18/2013.

\*\* Although it is possible that this black boxed warning and other changes were resulted from this FDAAA, the description of the study (as a source of evidence) in black boxed warning section is not specific enough. Also, this drug had 10 placebo-controlled trials and I am not confident concluding that this change was due to FDAAA #3. The FDA safety label change data doesn't specify the source of evidence either.

### NDA 22224, Trilipix (Choline Fenofibrate) 12/15/2008

(UNDETERMINED) NDA 22224-1, FDAAA #1 fulfilled 7/8/2011

An observational study to estimate the incidence and risk factors for hospitalized rhabdomyolysis in patients treated with a fibrate in combination with a statin, versus statin or fibrate monotherapy. This study will be conducted using a large, independent database that allows access to medical records to validate diagnoses. A recommended algorithm for identification of the inception cohorts of statin and fibrate users, estimation of person-time on drug, and identification of cases of rhabdomyolysis is provided in "Incidence of Hospitalized Rhabdomyolysis in Patients Treated with Lipid-Lowering Drugs" by Graham and Staffa, published in JAMA December 1, 2004.

4/27/2015 label updates on section 7 drug interactions:

“7.4 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates coadministered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine.”

\*\* There is no evidence that this change was based on FDAAA #1. NDA 22224 has REMS and the label was updated in 2015 and FDAAA #1 was officially fulfilled in 2011. No significant changes on rhabdomyolysis were found.

(NO CHANGE) NDA 22224, PMC #3, fulfilled 9/2/2010 final report 9/30/2009

Conduct a dose equivalence study of Trilipix (fenofibric acid) Delayed Release Capsules, to compare the pharmacokinetics of 3 x 45 mg Trilipix capsules against 1 x 135 mg Trilipix (fenofibric acid) Delayed Release Capsules.

\*\* No change was found regarding dosage 45 mg vs. 135 mg.

\*\*\* In the FDA postmarketing drug safety evaluation, adverse event reports of hepatic failure were identified and reviewed. None of these cases were fatal, and FDA determined that liver injury is adequately described in the current label as of December 2010. Adverse event reports of paradoxical decreases in high-density lipoprotein cholesterol were also noted. These cases lacked clinical details and information regarding concomitant drug use. FDA is continuing to evaluate the issue of paradoxical decreases in high-density lipoprotein cholesterol to determine if regulatory action is required. Since there is no evidence that the FDA did change label on decreased HDL cholesterol, this wouldn't change my judgment on FDAAA #1.

NDA 21176, Welchol (Colestevam Hydrochloride) 1/18/2008

(Changed) NDA 21176-17, PMC #3 fulfilled 7/12/2012

"To conduct drug-drug interaction testing between WelChol and the following drugs:

- \* a commonly used angiotensin converting enzyme (ACE) inhibitor
- \* a commonly used angiotensin receptor blocker (ARB)
- \* a long-acting beta-blocker
- \* aspirin
- \* rosiglitazone
- \* glimepiride
- \* glipizide ER
- \* sitagliptin
- \* metformin ER
- \* phenytoin

You have committed to the following time lines for in Vivo Studies for an ARB, glimepiride, glipizide ER, and phenytoin:

Protocol Submission: by June 30, 2008

Study Start: by September 30, 2008

Final Report Submission: by September 30, 2009

We note that you have committed to meet with the Agency in the first quarter of 2008 to determine a development plan for screening the remaining drugs listed above for potential interaction. Based on the results of this screen, you will conduct clinical drug interaction

studies for those drugs with the highest probability of an in vivo interaction with WelChol."

Letter on 7/9/2012 says:

"These "Prior Approval" supplemental new drug applications provide for revisions to the shared package insert. Specifically, the following sections have been revised: Highlights (Drug Interactions) Section 7 (Drug Interactions) Section 12.3 (Pharmacokinetics) Section 17 (Patient Counseling Information)

This supplement was submitted to fulfill a postmarketing commitment for the approved supplement -017 (NDA 21176). The specific commitment was to conduct drug-drug interaction testing between Welchol and the following drugs: • A commonly used ACE inhibitor (drug chosen; enalapril) • A commonly used angiotensin receptor blocker (drug chosen; olmesartan) • A long-acting beta-blocker (drug chosen; atenolol) • Aspirin • Rosiglitazone • Glimepiride • Sitagliptin • Metformin ER • Phenytoin We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text."

\*\* The letter confirms it.

(Changed) NDA 21176-17, PMC #1 fulfilled Q4 2013

To study WelChol as monotherapy treatment for type 2 diabetes mellitus.

6/28/2013 letter says:

Dear Ms. Borodanski:

Please refer to the following Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Welchol (colesevelam) Tablets [NDA 21176] and Oral Suspension [NDA 22362]:

NDA 21176/S-034

This supplement, submitted August 31, 2012, revises the ADVERSE REACTIONS (6.1 Clinical Studies Experience) and USE IN SPECIFIC POPULATIONS (8.5 Geriatric Use, *Type 2 Diabetes Mellitus* and 8.7 Renal Impairment) sections of the package insert to include results from study WEL-A-U305 entitled *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Welchol as Monotherapy for Type 2 Diabetes Mellitus*. This study was conducted in response to a postmarketing commitment (PMC) contained in the January 18, 2008, approval letter for Supplement -017.

NDA 21176/S-038

This supplement, submitted May 23, 2013, revises the DESCRIPTION and WARNINGS AND PRECAUTIONS sections of the shared package insert to include the correct amount of phenylalanine in the Oral Suspension formulation (13.5 mg and 27 mg for the 1.875 and 3.75 gram pouches, respectively).

\*\* Sections 5, 6, and 8 were changed. The letter confirms it.

(Changed) NDA 21176-17, PMC #2 fulfilled Q2 2014

To study WelChol in combination with thiazolidinediones as treatment for type 2 diabetes mellitus.

1/22/2014 letter says:

"These "Prior Approval" supplemental new drug applications propose updates to the package insert to include information from the study of Welchol as add-on therapy to pioglitazone for treatment of type 2 diabetes mellitus. This information was submitted in response to a postmarketing commitment for Supplement -017, which was approved January 18, 2008."

\*\* Sections 5, 6, and 8 were changed on 1/22/2014. The letter confirms it.

NDA 22148, Cymbalta (Duloxetine Hydrochloride)

(NO CHANGE) NDA 22148-1, PMC #3, fulfilled 10/3/2012

To conduct a randomized, double-blind, placebo-controlled study of Cymbalta at lower doses of 20 - 30 mg per day in the management of fibromyalgia.

\*\* No label has been changed for this NDA. Cymbalta has four NDAs (#21427, #21733, #22148, and #22516). NDA 21427 has most updated labels and I found no change in that NDA either.

NDA 22033, Luvox CR (Fluvoxamine Maleate) 1/25/2008

(UNDETERMINED) NDA 22033-1, PMC # fulfilled 5/14/2013

We note your commitment to conduct and provide a complete report of the microscopic examination of the remaining standard battery of tissues from the toxicity study entitled "Fluvoxamine Maleate: 14-Day Oral (Gavage) Administration Comparative Toxicity Study in the Rat with Fluvoxamine Maleate and Fluvoxamine Maleate Spiked with 3% Fluvoxketone and 10% Fluvoxamine Addition Product".

\*\* In 2018, animal juvenile (young dogs and rats) toxicity study results were added, but there's no information that would fit this study description.

NDA 22157, Xyzal (Levocetirizine Dihydrochloride) 1/28/2008

(Changed) NDA 22157-1, PREA #2 fulfilled Q4 2009

Deferred pediatric study under PREA for the treatment of Chronic Idiopathic Urticaria in pediatric patients ages 6 months to < 6 years.

8/21/2009 letter says:

“This supplemental new drug application provides for the use of Xyzal (levocetirizine dihydrochloride) 0.5mg/ml oral solution and 5mg tablets for the relief of symptoms associated with seasonal allergic rhinitis (SAR) in children 2 years of age and older, and for the relief of symptoms of perennial allergic rhinitis (PAR) and treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) for children 6 months of age and older.”

8/21/2009 label updates in indications:

Seasonal Allergic Rhinitis

XYZAL® is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older.

Perennial Allergic Rhinitis

XYZAL is indicated for the relief of symptoms associated with perennial allergic rhinitis in adults and children 6 months of age and older.

Chronic Idiopathic Urticaria

XYZAL is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older.

\*\* Sections 1, 2, 4, 6, and 8 were updated about pediatric patients. Although the letter doesn't say about the source of evidence, specific age groups and indications fit the description of the PREA #1, 2, and 3 studies. Also, these PREA studies were fulfilled in the same time period.

(Changed) NDA 22157-1, PREA #1 fulfilled Q4 2009

Deferred pediatric study under PREA for the treatment of Perennial Allergic Rhinitis in pediatric patients ages 6 months to < 6 years.

\*\* See the letter and label updates in PREA #2 above. Sections 1, 2, 4, 6, and 8 were updated about pediatric patients. Specific age groups and indications fit the description of the PREA #1, 2, and 3 studies.

(Changed) NDA 22157-1, PREA #3 fulfilled Q4 2009

Deferred pediatric study under PREA for the treatment of Seasonal Allergic Rhinitis in pediatric patients ages 2 years to < 6 years.

\*\* See the letter and label updates in PREA #2 above. Sections 1, 2, 4, 6, and 8 were updated about pediatric patients. Specific age groups and indications fit the description of the PREA #1, 2, and 3 studies.

NDA 21926, Treximet (Naproxen Sodium; Sumatriptan Succinate) 4/15/2008

(UNDETERMINED) NDA 21926-1, FDAAA #3 fulfilled 2/17/2011

A randomized, double-blind, active comparator clinical trial of Treximet in adults with episodic migraine dosed with either Treximet, naproxen sodium 500 mg, or sumatriptan 85 mg to further assess the hypertensive effects of Treximet relative to each of its two active ingredients.

5/9/2016 label updates:

“Boxed Warning

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

Cardiovascular Thrombotic Events

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.

{Product} is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.”

\*\* Label updates data in early 2011 are not available for this NDA. On 11/14/2011, cardiovascular risks were updated, but it is uncertain that this change was based on this FDAAA.

\*\*\* Black boxed warning  
(<https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=208>) was added on 05/09/2016, but it was a class action on NSAID and it is unclear whether this FDAAA led to boxed warning.

On 7/9/2015, FDA announced (<https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm>):

“The U.S. Food and Drug Administration (FDA) is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke. Based on our comprehensive review of new safety information, we are requiring updates to the drug labels of all prescription NSAIDs. As is the case with current prescription NSAID labels, the Drug Facts labels of over-the-counter (OTC) non-aspirin NSAIDs already contain information on heart attack and stroke risk. We will also request updates to the OTC non-aspirin NSAID Drug Facts labels.

...

The risk of heart attack and stroke with NSAIDs, either of which can lead to death, was first described in 2005 in the Boxed Warning and Warnings and Precautions sections of the prescription drug labels. Since then, we have reviewed a variety of new safety information on prescription and OTC NSAIDs, including observational studies, a large combined analysis of clinical trials, and other scientific publications. These studies were also discussed at a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee held on February 10-11, 2014.”

---- Sources include

Food and Drug Administration [Internet]. Silver Spring, MD. FDA Briefing Information for the February 10-11, 2014 Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available from:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM383180.pdf>. Accessed December 23, 2014.

Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769-79.

Source #2 is a meta-analysis of 280 trials of NSAIDs versus placebo (124,513 participants, 68,342 person-years) and 474 trials of one NSAID versus another NSAID (229,296 participants, 165,456 person-years). In source #1, I didn't find “sumatriptan” in FDA briefing document. Since source # is a meta analysis, it is challenging to judge whether this FDAAA study has influenced BBW decision.

(Changed) NDA 21926-1, PREA #1 fulfilled 5/14/2015

Conduct a controlled effectiveness study of Treximet for the acute treatment of migraine attacks with or without aura in pediatric patients ages 12 years to 17 years.

5/14/2015 letter says:

“This Prior Approval supplemental new drug application proposes sumatriptan/naproxen for the acute treatment of migraine with or without aura in adolescents 12 to 17 years old.

.....

We refer to the deferred pediatric studies noted in our original approval letter dated April 15, 2008:

1277-1 Conduct a controlled effectiveness study of Treximet for the acute treatment of migraine attacks with or without aura in pediatric patients ages 12 years to 17 years.

1277-2 Conduct a long-term open label safety study in pediatric patients with migraine ages 12 years to 17 years. We have reviewed your supplemental application and conclude that the above requirements were fulfilled.”

\*\* Sections 1, 2, 5, 6, and 8 were updated accordingly. Although the letter on 5/14/2015 doesn't say the revision was based on these PREA studies, the FDA reviewed these studies and concluded that they were fulfilled in this supplemental approval. Also, the changes fit the descriptions of these studies.

(Changed) NDA 21926-1, PREA #2 fulfilled 5/14/2015

Conduct a long-term open label safety study in pediatric patients with migraine ages 12 years to 17 years.

\*\* Sections 6 and 8 were updated accordingly. Although the letter on 5/14/2015 doesn't say the revision was based on these PREA studies, the FDA reviewed these studies and concluded that they were fulfilled in this supplemental approval. Also, the changes fit the descriptions of these studies.

NDA 22047, Seroquel XR (Quetiapine Fumarate), 10/8/2008

(Changed) NDA 22047-6, PREA #1 fulfilled 4/30/2013

Deferred pediatric study under PREA for the use of Seroquel XR as monotherapy in the treatment of bipolar depression.

4/30/2013 letter:

"These "Prior Approval" supplemental new drug applications propose incorporation of safety data from a trial in children and adolescents with bipolar depression."

4/30/2013 label updates:

Section 5

"Children and Adolescents: Safety and effectiveness of SEROQUEL XR is supported by studies of SEROQUEL in children and adolescent patients 10 to 17 years of age [see Clinical Studies (14.1 and 14.2)]. In a placebo-controlled SEROQUEL XR monotherapy study (8 weeks duration) of children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the percentage of children and adolescents with shifts in total cholesterol ( $\geq 200$  mg/dL), triglycerides ( $\geq 150$  mg/dL), LDL-cholesterol ( $\geq 130$  mg/dL) and HDL-cholesterol ( $\leq 40$  mg/dL) from baseline to clinically significant levels were: total cholesterol 8% (7/83) for SEROQUEL XR vs. 6% (5/84) for placebo; triglycerides 28% (22/80) for SEROQUEL XR vs. 9% (7/82) for placebo; LDL-cholesterol 2% (2/86) for SEROQUEL XR vs. 4% (3/85) for placebo and HDLcholesterol 20% (13/65) for SEROQUEL XR vs 15% (11/74) for placebo."

The FDA says "The efficacy and safety of Seroquel® and Seroquel XR® in the treatment of bipolar depression was not established in children and adolescents ages 10 to 17 years is supported by one 8-week, double-blind, placebo controlled trial with Seroquel XR®"  
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM495273.pdf>

\*\* Sections 5, 6, and 8 were updated. The FDA says these PREA studies were fulfilled on 4/30/2013.

(Changed) NDA 22047-7, PREA #1 fulfilled 4/30/2013

Deferred pediatric study under PREA for the use of Seroquel XR as monotherapy in the treatment of bipolar mania.

4/30/2013 label changes:

Section 5

"In a placebo-controlled SEROQUEL monotherapy study of adolescent patients (13–17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL (n=138) compared to placebo (n=67) was –0.75 mg/dL versus –1.70 mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescent patients (10–17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for SEROQUEL (n=170) compared to placebo (n=81) was 3.62 mg/dL versus –1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level ( $<100$  mg/dL) or a baseline borderline fasting glucose level ( $\geq 100$  mg/dL and  $<126$  mg/dL) had a treatment-emergent blood glucose level of  $\geq 126$  mg/dL.  
...."

FDA says "The efficacy and safety of Seroquel® and Seroquel XR® in the treatment of bipolar mania in children and adolescents ages 10 to 17 years is supported by one 3-week, double-blind, placebo controlled trial with Seroquel®"  
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM495273.pdf>

\*\* according to the FDA, pediatric labeling was changed twice: December 2, 2009 and April 30, 2013. But, indication was not changed on December 2, 2009—until April 30, 2013, in the black boxed warning section, it was noted that “SEROQUEL XR is not approved for use in pediatric patients” and the warning “Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years” appeared multiple times throughout the label. April 30, 2013 label change was a major change including indications. Sections 1, 5, 6, and 8 were updated. Although 4/30/2013 letter mentions “bipolar depression” only, warnings, adverse reactions, and specific subpopulation data were changed concerning “bipolar mania” for pediatric patients.

#### NDA 22008, Requip XL (Ropinirole Hydrochloride) 6/13/2008

(Changed) NDA 22008-1, FDAAA #1, fulfilled Q2 2016

Conduct a fixed-dose, placebo-controlled, double-blinded study that examines multiple doses in early Parkinson's disease. The trial should identify a range of doses inclusive of the lowest effective dose and the lowest maximally effective therapeutic dose.

3/23/2017 letter says:

“This Prior Approval supplemental new drug application provides for updates to the Requip XL product labeling to (1) incorporate information from two dose-response post-marketing requirement (PMR) studies and (2) comply with the Pregnancy and Lactation Labeling Rule (PLLR). Specifically, the study reports referenced in this supplement are responsive to the following fulfilled PMRs:

- PMR 1005-1:GSK Study Number: ROP111662, A fixed-dose, dose-response study for ropinirole prolonged release (PR) in patients with early stage Parkinson’s disease [Report No.: 2014N201874\_00]
- PMR 1005-2:GSK Study Number: ROP111569, A fixed dose, dose-response study for ropinirole prolonged release (PR) as adjunctive treatment to L-dopa in patients with advanced Parkinson's disease [Report No.: 2014N225778\_01]”

On 3/23/2017 label, sections 2 and 5 were updated.

\*\* The letter confirms the change.

(Changed) NDA 22008-1, FDAAA #2, fulfilled Q4 2016

Conduct a fixed-dose, placebo-controlled, double-blinded study that examines multiple doses in late Parkinson's disease. The trial should identify a range of doses inclusive of the lowest effective dose and the lowest maximally effective therapeutic dose.

\*\* See FDAAA #1. The letter confirms the change.

(NO CHANGE) NDA 22008-1, PMC #3 fulfilled Q3 2014 – fulfilled June 10, 2014

"Evaluate whether ropinirole is a P-gp substrate and/or inducer for major CYP enzymes (e.g., CYP3A4) and, if so, any drug-drug interaction potential through either mechanism. This can be accomplished through a comprehensive literature review or by conducting an in vitro study."

8/28/2014 letter says:

“We also note this approval includes the addition of results from your postmarketing commitment (PMC) study to evaluate whether ropinirole is a P-gp substrate and/or inducer for major CYP enzymes, for which a PMC Fulfilled letter was issued on June 10, 2014.”

\*\* 8/28/2014 label updates section 12 and the letter confirms this is a change based on this PMC. But changes in section 12 are not considered major changes.

\*\*\* Reports of fatigue, asthenia (weakness), and malaise were identified and reviewed, according to the FDA Postmarketing Drug Safety Evaluation Summaries Completed from January 2010 through September 2010. FDA said FDA is continuing to evaluate these issues to determine if regulatory action is required as of 2011. PMR/PMCs associated with NDA 22008 in 2008 seems to be unrelated to this evaluation.

#### NDA 21911, BANZEL (RUFINAMIDE) 11/14/2008

(NO CHANGE) NDA 21911-1, FDAAA #3 fulfilled Q3 2014

Conduct a juvenile dog toxicology study to identify the unexpected serious risk of adverse effects on postnatal growth and development.

\*\* No data was updated on postnatal growth and development and no mention on juvenile dog toxicology study.

(NO CHANGE) NDA 21911-1, FDAAA #1 fulfilled Q3 2013

"Conduct additional analyses to further examine the effect of Banzel (rufinamide) on the QT interval, specifically studying its effect in patients receiving concomitant medications that may also shorten the QT interval. For clinical trials AE/ET1 and CRUF331-0022 (and any other trials in which patients were treated with medications other than rufinamide and in which QT data was collected), please provide the following:

a. The baseline (pre-treatment) mean QT interval (as measured by all three correction methods) in rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (listed below) and in patients without such concomitant medications.

b. The mean on-treatment QT interval (again by all three correction methods) for rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval and in patients without such concomitant medications.

Conduct the same analysis for sodium channel blocking drugs. See AP letter for list of drugs."

\*\* No major data on QT was changed.

(NO CHANGE) NDA 21911-1, FDAAA #2 fulfilled 1/29/2009 (per letter 3/27/2009)

Conduct an in vitro metabolism study to characterize the potential serious safety risk of the inhibitory effect of Banzel (rufinamide) on P-gp.

11/8/2010 label updates:

Section 12

"Rufinamide did not show any significant inhibition of P-glycoprotein in an in-vitro study."

\*\* On 11/8/2010, section 12 was changed in the label based on this study. But, not a major change.

NDA 21745, Ryzolt (Tramadol Hydrochloride) 12/30/2008

(UNKNOWN) NDA 21745-1, FDAAA #2 disappeared since Q1 2017

"A clinical trial in healthy adult volunteers to assess the risk of QT prolongation with tramadol, i.e., a thorough QT (tQT) trial. This trial will provide information on cardiac depolarization and conduction effects of tramadol at therapeutic and supratherapeutic dose regimens. The tQT trial may be conducted as part of the multiple ascending dose trial."

\*\* This FDAAA requirement was not in the approval letter, but in the system (FDA PMR/PMC database). It could be that PM studies were stated in a separate letter. Status is unknown because this FDAAA requirement disappeared since Q1 2017.

(UNKNOWN) NDA 21745-1, FDAAA #1 disappeared since Q1 2017

"A multiple ascending dose clinical trial in healthy adult volunteers to determine the maximum tolerated dose of tramadol and to inform the dosing for a thorough QT trial of tramadol."

\*\* This FDAAA requirement was not in the approval letter, but in the system (FDA PMR/PMC database). It could be that PM studies were stated in a separate letter. Status is unknown because this FDAAA requirement disappeared since Q1 2017.

NDA 19655, 19910, 20518 RETROVIR (ZIDOVUDINE) 9/19/2008

(Changed) NDA 19655-46, 19910-33, 20518-16, PREA, fulfilled 11/6/2009

Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 1 month to < 6 weeks of age. Please assess zidovudine pharmacokinetic data in neonates and use pharmacokinetic modeling and



simulation data to propose dosing recommendations for HIV-1 infected children between 1 month and < 6 weeks of age.

11/6/2009 letter says:

“These “prior approval” supplemental new drug applications update the package inserts with pediatric dosing information for the RETROVIR syrup and the “Patient Counseling” section with information related to HIV-1/HCV co-infection, lactic acidosis/hepatomegaly and myopathy.”

NDA 19910 11/6/2009 letter adds:

“We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.”

11/6/2009 label updates:

“section 2

Pediatric Patients (4 weeks to <18 years of age): Healthcare professionals should pay special attention to accurate calculation of the dose of RETROVIR, transcription of the medication order, dispensing information, and dosing instructions to minimize risk for medication dosing errors. Prescribers should calculate the appropriate dose of RETROVIR for each child based on body weight (kg) and should not exceed the recommended adult dose. Before prescribing RETROVIR capsules or tablets, children should be assessed for the ability to swallow capsules or tablets. If a child is unable to reliably swallow a RETROVIR capsule or tablet, the RETROVIR syrup formulation should be prescribed. The recommended dosage in pediatric patients 4 weeks of age and older and weighing  $\geq 4$  kg is provided in Table 1. RETROVIR Syrup should be used to provide accurate dosage when whole tablets or capsules are not appropriate.”

\*\*\* Specific dosing information for pediatric patients.

2/24/2017 black box warning:

“Boxed Warning

Additions underlined:

**WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS”**

\*\*\* Unclear what led to the black box warning, but it is unlikely that this PREA had resulted in adding BBW. And this is just wording changes. The BBW on hepatomegaly with steatosis was already present at the time of 2008

**NDA 22185, Taclonex (Betamethasone Dipropionate; Calcipotriene Hydrate) 8/29/2008**

(Changed) NDA 22185-1, PREA, fulfilled 8/29/2014

Conduct a study in pediatric patients ages 12 to 17 years of TACLONEX SCALP Topical Suspension for the treatment of scalp psoriasis. Enrollment should be sufficient to allow for 100 evaluable patients.

Evaluate the effect of TACLONEX SCALP Topical Suspension on calcium metabolism in all subjects and on the hypothalamic-pituitary axis in a subset of 30 patients.

8/29/2014 letter says:

“This “Prior Approval” supplemental new drug application provides for an extension of the approved indication to include patients ages 12 to 17 years with plaque psoriasis of the scalp.

...

We note that you have fulfilled the pediatric study requirement for patients ages 12 to 17 years with plaque psoriasis of the scalp for this application. We have reviewed your submission and conclude that the below requirement was fulfilled.

808-1 Conduct a study in pediatric patients ages 12 to 17 years of Taclonex Topical Suspension for the treatment of scalp psoriasis. Enrollment should be sufficient to allow for 100 evaluable patients. Evaluate the effect of Taclonex Topical Suspension on calcium metabolism in all subjects and on the hypothalamic-pituitary axis in a subset of 30 patients.”

\*\*\* Sections 1, 2, 6, and 8 were updated on 8/29/2014 label regarding pediatric patients 12-17 years.

(NO CHANGE) NDA 22185-1, FDAAA, fulfilled Q3 2014 (final report Q1 2014)  
Evaluate the carcinogenic potential of calcipotriene in a two-year oral study in rats.

\*\*\* Section 13 was updated on 8/29/2014. It is not considered a major change.

#### NDA 22369, Latisse (Bimatoprost) 12/24/2008

(Changed) NDA 22369, PREA #1 fulfilled 4/21/2014 (final report 3/4/2014)

Deferred pediatric study under PREA for the treatment of hypotrichosis in pediatric patients ages 0 to 17 years.

9/4/2014 letter says:

“We are waiving the pediatric study(ies) requirements for ages less than 5 years old because the necessary studies are impossible or highly impracticable. This product is appropriately labeled for use in pediatric population ages  $\geq 5$  to 17 years. Therefore, no additional pediatric studies are needed at this time.

....

S-010, received March 4, 2014, which provides for the revision of the 8.4 Pediatric Use section to the Package Insert.”

\*\* 9/4/2014 label was updated on pediatric patients (section 8).

(NO CHANGE) NDA 22369-1, PMC #2 fulfilled Q2 2014

To perform a four month, randomized, controlled, comparative study of Latisse (bimatoprost ophthalmic solution) 0.03% in at least 50 African American subjects.

\*\* No specific information on race (African American) was updated.

#### NDA 22212, Durezol (Difluprednate) 6/23/2008

(Changed) NDA 22212-1, PREA #1 fulfilled 3/22/2013

Deferred pediatric study under PREA for the treatment of treatment of post-operative inflammation following cataract surgery in pediatric patients aged 0 to 3 years of age undergoing cataract surgery.

3/22/2013 letter says:

“This “Prior Approval” supplemental new drug application provides for revisions to the Pediatric Use section of the package insert to reflect the results from Clinical Study C-10-004 entitled, “A Phase 3B, Multicenter, Randomized, Double-Masked, Parallel-Group, Active-Controlled Study of the Safety and Efficacy of Difluprednate Ophthalmic Emulsion, 0.05% (Durezol) 4 Times Daily (QID) and Prednisolone Acetate Ophthalmic Suspension, 1.0% (Pred Forte) QID for the Treatment of Inflammation Following Cataract Surgery in Children 0 to 3 Years of Age.

....

We note that this supplemental application contains the final report for the following postmarketing requirement listed in the June 23, 2008, approval letter.

1444-1 A study of pediatric patients 0 to 3 years of age for the treatment of post-operative inflammation following cataract surgery We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all of your postmarketing requirements acknowledged in our June 23, 2008, letter.”

3/22/2013 label updates on section 8:

“8.4 Pediatric Use DUREZOL was evaluated in a 3-month, multicenter, double-masked, trial in 79 pediatric patients (39 DUREZOL; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL to prednisolone acetate ophthalmic suspension, 1%.”

\*\*\* The letter identifies a phase 3B study as the source of evidence and PREA study #1 was fulfilled.

(UNDETERMINED) NDA 22212-1, PMC # -- not available in the dataset  
post-marketing study of difluprednate in pediatric subjects

\*\*\* This study description is not specific enough to see whether a change is from this study.

#### NDA 21797, 21798 Baraclude (Entecavir) 7/25/2008

(NO CHANGE) NDA 21797-5, 21798-6, PMC #1 fulfilled Q2 2010 (final report 6/30/2009)

Evaluate the contribution of the rtF88Y amino acid substitution, individually and in combination with the primary ETVr- and LAMr-associated substitutions, to BARACLUDE resistance (including cell culture susceptibility to ETV and replication capability) by site-directed mutagenesis.

\*\* No information on rTF88Y was found.

#### NDA 22023, Emend (Fosaprepitant Dimeglumine) 1/25/2008

(NO CHANGE) NDA 22023-1, PMC #2 fulfilled Q4 2009 (final report 7/31/2008)

Further characterize the effects of fosaprepitant on blood pressure.

\*\* No information on blood pressure was found.

\*\*\* According to the FDA postmarketing drug safety evaluation, adverse event reports of infusion site reactions were identified. Some of these reactions were serious, involving swelling and redness of the entire arm. FDA is continuing to evaluate these issues to determine if the current labeling, which includes these events in the Warnings and Precautions section, is adequate as of June 2011. This has no relation to the PMC #2.

#### NDA 21830, ASACOL HD (MESALAMINE) 5/29/2008

(Changed) NDA 21830-1, PREA #, fulfilled 10/18/2013 (final report 1/15/2011)

Conduct a study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation (i.e., an oral mesalamine formulation appropriate for pediatric dosing), such as your approved product, Asacol. The study will evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study will be a randomized, double-blind study comparing at least two different dose levels of mesalamine and it will enroll at least 40 pediatric patients in each dosing arm.

10/18/2013 letter says:

“This “Prior Approval” supplemental new drug application proposes the addition of information to the pediatric use section of the prescribing information.

...

We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

319-1 Conduct a study in pediatric patients ages 5 to 17 years with ulcerative colitis using an....

We have reviewed your submission and conclude that the above requirement was fulfilled.”

\*\* Although the letter says there has been a change on pediatric use section, no data was updated in the label. But, there are three products with the ingredient Mesalamine: Asacol, Asacol HD and Delzicol. And, Asacol (NDA 19651) and Delzicol (NDA 204412) were approved for use of mesalamine for patients  $\geq 5$  years old in 2013 based on this study. Sections 1 and 2 were changed.

#### NDA 21861 Patanase (Olopatadine Hydrochloride) 4/15/2008

(Changed) NDA 21861-1, FDAAA #, fulfilled 2/24/2012 (final report 8/16/2011)

A one-year, controlled clinical trial in patients with perennial allergic rhinitis to assess the long term safety of povidone-free olopatadine hydrochloride nasal spray with respect to nasal septal perforation. We also request that you assess the long term safety of this product with respect to local nasal adverse effects, including epistaxis and nasal ulceration, as well as systemic effects. Include at least the following three treatment groups: povidone-free olopatadine hydrochloride nasal spray, vehicle placebo with pH matching olopatadine hydrochloride nasal spray, and vehicle placebo with normal pH to evaluate if the low pH of the formulation has an effect on local nasal safety. Submit a labeling supplement reflecting the results of the clinical trial.

Actual Primary Completion Date: January 2011 (clinicaltrials.gov)

Actual Study Completion Date: January 2011 (clinicaltrials.gov)

2/22/2012 letter says:

“This Prior Approval supplemental new drug application provides for revisions to the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS-Clinical Trial Experience sections of the package insert to reflect the results of the Post Marketing Trial "Safety of Patanase®" Nasal Spray in Patients with Perennial Allergic Rhinitis" ( C-08-32), and the addition of information regarding anosmia and hyposmia ADVERSE REACTIONS-Post Marketing Experience section of the package insert.”

\*\* Sections 5 and 6 were updated based on this trial. When this NDA was approved on 4/15/2008, the FDA stated that “FDA has determined that you are required to conduct a postmarketing clinical trial of Patanase Nasal Spray to assess this signal of a serious risk.” And that trial was this FDAAA #1.

(Changed) NDA 21861-1, PREA #, fulfilled 12/1/2009 (final report 7/1/2009)

Deferred pediatric study under PREA for the treatment of allergic rhinitis in pediatric patients ages 2 to 11 years of age.

12/1/2009 letter says:

“This Prior Approval supplemental new drug application provides for the use of Patanase (olopatadine hydrochloride) Nasal Spray 0.6% for the treatment of symptoms of seasonal allergic rhinitis in patients 6 to 11 years of age.

....

We note that you have fulfilled the pediatric study requirement for ages 2-11 of age for this application. This product label has information covering ages 2 to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.”

12/1/2009 label updates: sections 1, 2, 6, 8, and 12

Section 6

“The safety data from pediatric patients 6-11 years of age are based upon 3 clinical trials in which 870 children with seasonal allergic rhinitis (376 females and 494 males) were treated with PATANASE Nasal Spray 1 or 2 sprays per nostril twice daily for 2 weeks. The racial distribution of pediatric patients receiving PATANASE Nasal Spray was 68.6% white, 16.6% black, and 14.8% other. The incidence of discontinuation due to adverse reactions in these controlled clinical trials was comparable for PATANASE Nasal Spray and vehicle nasal spray. Overall, 1.4% of the 870 pediatric patients across all 3 studies treated with PATANASE Nasal Spray and 1.3% of the 872 pediatric patients treated with vehicle nasal spray discontinued due to adverse reactions. Safety information for pediatric patients 2 to 5 years of age is obtained from one vehicle-controlled study of 2 weeks duration [See Pediatric Use (8.4)].”

Section 8

“The safety of PATANASE Nasal Spray at a dose of 1 spray per nostril twice daily was evaluated in one 2 week vehicle-controlled study in 132 children ages 2 to 5 years of age with allergic rhinitis. In this trial, 66 patients ( 28 females and 38 males) were exposed to PATANASE Nasal Spray. The racial distribution of patients receiving PATANASE Nasal Spray was 66.7% white, 27.3% black, and 6.4% other. Two patients exposed to vehicle nasal spray discontinued due to an adverse reaction (1 patient with pneumonia and 1 patient with rhinitis) compared to no patients exposed to PATANASE Nasal Spray. The most common (greater than 1.0%) adverse events reported were diarrhea (9.1%), epistaxis (6.1%), rhinorrhea (4.5%), bitter taste (3.0%) and wheezing (3.0%). Diarrhea was reported less frequently (< 1%) in the 6 to 11 year old age group. The incidence of epistaxis was higher in the pediatric population (5.7% in 6 -11 year old patients and 6.1% in 2-5 year old patients) compared to the adult and adolescent population (3.2%).”

12/1/2009 FDA review document says:

“After reformulation of the product, the applicant submitted a revised pediatric development plan in January of 2007, discussed the plan with the Division in February, and submitted a PPSR in March of 2007, requesting that the Agency issue a pediatric Written Request to study children below 12 years of age. The Division concluded that removal of povidone was adequate to assure reasonable safety so that pediatric studies could be conducted. A Written Request was issued on July 19, 2007, asking for two studies with Patanase in patients 2 through 11 years of age. The decision to issue the Written Request for Patanase was made with concurrence of the CDER Pediatric Implementation Team (PdIT) [reviewed the Written Request] and

the Division of Anti-Infective Ophthalmology Products [because of the ophthalmologic formulation of olopatadine]. In the end, the Written Request only contained the two Patanase studies that are submitted with this supplement, a 2-week safety and efficacy trial in patients 6- 11 years of age, and a 2-week safety and pharmacokinetics trial in patients 2-5 years of age. The Written Request is attached as an Appendix to this Review.

.....

The NDA approval letter contains the PMR for pediatric studies with a submission date of July 1, 2009, without specifics for the studies because the Division had previously discussed the pediatric development plan with Alcon and the Division was aware that the first of the pediatric studies was being already performed in response to the Written Request. The Division set the PREA date for these studies to match the BPCA date, July 1, 2009. With this submission, the PREA PMR is considered fulfilled.”

\*\*\* Sections 1, 2, 6 and 8 were updated based on this PREA study.

#### NDA 21372, Aloxi (Palonosetron Hydrochloride) 2/29/2008

(changed) NDA 21372-8, PREA #, fulfilled 5/27/2014

Deferred pediatric study under PREA to evaluate (1) the safety and tolerability of two doses of I.V. palonosetron for the prevention of postoperative nausea and vomiting, and (2) the efficacy of these two I.V. palonosetron doses to prevent postoperative nausea and vomiting.

5/27/2014 letter says:

**Prior Approval supplemental new drug application S-018 provides for updates to the Use in Specific Populations section of the package insert. The agreed-upon labeling changes reflect the lack of efficacy in the pediatric patient population.**

**Prior Approval supplemental new drug application S-019 provides for the prevention of nausea and vomiting associated with cancer chemotherapy in pediatric patients 1 month and older.**

“We have received your submissions dated November 27 and 28, 2013, reporting on the following postmarketing requirements listed in the February 29, 2008 approval letter and August 3, 2005 Pediatric Deferral granted letter.

120-1 Deferred pediatric study under PREA to evaluate (1) the safety and tolerability of two doses of I.V. palonosetron for the prevention of postoperative nausea and vomiting, and (2) the efficacy of these two I.V. palonosetron doses to prevent postoperative nausea and vomiting.

806-1 Deferred pediatric study under PREA for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy (CINV) in pediatric patients 1 month to 17 years of age.

806-2 Deferred pediatric study under PREA for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV) in pediatric patients 1 month to 17 years of age.

We have reviewed your submission and conclude that the above requirements were fulfilled. This completes all of your postmarketing requirements acknowledged in our August 3, 2005 and February 29, 2008 letters.”

\*\* Sections 1, 2, and 8 were updated. Letter confirms these studies.

#### NDA 125147, VECTIBIX (PANITUMUMAB) 6/23/2008

(Changed) NDA 125147-26, FDAAA #2, fulfilled Q4 2011

To complete and provide a final Clinical Trial Report for Study 20050203: First-line Treatment entitled, "A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/ 5-fluorouracil/leucovorin to the Efficacy of Oxaliplatin/5-fluorouracil/leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer," including a final analysis of any significant toxicities that have occurred during the treatment period. This analysis is necessary to assess the signal of a serious risk, decreased survival with the concomitant use of panitumumab (Vectibix) and chemotherapy. The final report submission will include the primary datasets and programs used for generation of analyses; analyses will include, but may not be limited to, the analyses described in the statistical analysis plan.

Study	Completion	Date:	March	2013
Primary Completion Date: August 2009 (Final data collection date for primary outcome measure)				

8/17/2012 letter:

“This “Changes Being Effected” labeling supplement to your biologics license application includes the following: • An addition of a new INDICATIONS AND USAGE subsection; Limitation of Use, regarding KRAS mutation positive mCRC status. • A revised WARNINGS and PRECAUTIONS subsection, Increased Mortality or Toxicity with Vectibix in Combination with Chemotherapy, to improve clarity. • A revised WARNINGS AND PRECAUTIONS subsection, Dermatologic Toxicity, to improve clarity.

This “Prior Approval Supplement” labeling supplement to your biologics license application revised the ADVERSE REACTIONS, Immunogenicity (6.2) subsection to include additional updated monotherapy immunogenicity data and immunogenicity data from patients receiving irinotecan- or oxaliplatin-based chemotherapy.”

#### Section 5:

“In a randomized, open-label study enrolling 440 patients with KRAS mutation-positive mCRC; evaluating Vectibix in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy for mCRC, shortened overall survival time was observed in the mutant KRAS mCRC population after 294 deaths (HR=1.24, 95% CI: 0.98-1.57).”

#### Section 1:

Vectibix is not indicated for the treatment of patients with KRAS mutation-positive mCRC or for whom KRAS mCRC status is unknown. Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had KRAS mutations in codon 12 or 13 [see Warnings and Precautions (5.3), Clinical Pharmacology (12.1), and Clinical Studies (14.3)].

In section 14, a new section was added (14.3 Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients with mCRC Containing KRAS Mutations)

\*\*\* Both FDAAA #2 (study 20050203/PRIME/the first line) and PMC #3 (study 20050181/the second line) were fulfilled in Q4 2011 according to the FDA database. No specific fulfillment date was updated. Both 20050181 and 20050203 are pivotal studies for approval. 20050181 study 1:1 randomized to FOLFIRI (fluorouracil, leucovorin, and irinotecan), stratified by prior bevacizumab (Avastin) treatment. 20050203 (study 3 in the label) did randomize 1:1 to FOLFOX (fluorouracil, leucovorin, and oxaliplatin) in the first line therapy.

\*\*\* KRAS mutation was reviewed in both PRIME and 20050181 studies.

\*\*\* Although the letter doesn't specify the source of evidence, the label was updated based on study 20040203 which was randomized to FOLFOX in the first line therapy.

(UNDETERMINED) NDA 125147-26, PMC #3 fulfilled Q4 2011

To provide a study report containing a final analysis of any significant toxicities that have occurred during the treatment period for study 20050181 entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer." The final report submission will include the primary datasets and programs used for the generation of analyses; analyses will include, but may not be limited to, the analyses described in the statistical analysis plan.

Study	Completion	Date:	November	2010
Primary Completion Date: April 2009 (Final data collection date for primary outcome measure)				

\*\*\* Although it is likely that study 20050181 was used as a source of evidence in label change, but I can't provide evidence because the study connotation used in the labels is somewhat unclear. It is not clear that study 2 mentioned in the label refers this study 20050181. Study 20050181 is for the second line therapy, but study 2 mentioned in the label says “a randomized, open-label, multicenter trial in the first-line treatment of mCRC. Patients (n = 1053) were randomized 1:1 to Vectibix at a dose of 6 mg/kg given once every 2 weeks, in combination with bevacizumab and an

oxaliplatin- or irinotecan-based 5-fluorouracil-containing chemotherapy regimen, or to bevacizumab and chemotherapy alone.”

See comments above for FDAAA #2.

#### NDA 22161, LEXISCAN (REGADENOSON) 4/10/2008

(Changed) NDA 22161-1, FDAAA #1, fulfilled 10/17/2011

A clinical trial to examine the pulmonary adverse effects of a single 0.4mg dose of Lexiscan in approximately 600 patients with a broad severity of bronchoconstrictive disease (300 with asthma, 300 with COPD). Patient follow-up for the detection of adverse reactions will extend over a time period of at least 24 hours following Lexiscan administration.

9/23/2011 letter says:

“NDA 22161/S-006 dated June 7, 2011, received: June 8, 2011. The June 7, 2011, submission constituted a complete response to our May 24, 2011, action letter. The supplement was submitted November 24, 2010. S-006: This “Prior Approval” supplemental new drug application provides for revisions to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, USE in SPECIFIC POPULATIONS AND PHARMACODYNAMICS sections of the packet insert to include data obtained from the Post-Marketing Requirement safety studies (3606-CL-3001 and 3606-CL-3010). • NDA 22161/S-007 and S-008 dated March 31, 2011, received March 31, 2011. We acknowledge receipt of your amendment dated April 13, 2011. S-007: This “Changes Being Effected” supplemental new drug application provides for revisions to the ADVERSE REACTIONS section of the packet insert to include data reported through post-marketing safety surveillance and adverse event reports of hypersensitivity and QTc prolongation. S-008: This “Prior Approval” supplemental new drug application provides for revisions to the PHARMACODYNAMICS section of the packet insert to include language regarding the ingestion of caffeine prior to subjects undergoing myocardial perfusion imaging (MPI).”

\*\*\* Sections 5, 6, and 8 were updated based on FDAAA #1 (study 3606-CL-3001) and FDAAA #2 (study 3606-CL-3010). The letter confirms the changes.

(Changed) NDA 22161-1, FDAAA #2 fulfilled 10/17/2011

A clinical trial to examine the serious adverse effects of a single 0.4mg dose of Lexiscan in approximately 300 patients with moderate (or worse) chronic kidney disease (Stage 3 or greater/using NKF GFR definitions). Patient follow-up for the detection of adverse reactions will extend over a time period of at least 24 hours following Lexiscan administration.

\*\*\* See comments on FDAAA #1.

\*\*\* According to the FDA postmarketing safety evaluation, Serious adverse event reports of cardiovascular events, respiratory events, headache/migraine headache, and infusion site reactions were identified. All non-cardiovascular event reports were reviewed and there was no association of the adverse events with Lexiscan. FDA is continuing to evaluate cardiovascular events to determine if regulatory action is required. It is unclear that these reports were from these FDAAA studies. Nonetheless, these FDAAA safety studies brought label changes.

#### NDA 22104 VENLAFAXINE HYDROCHLORIDE, 5/20/2008

(unknown) NDA 22104-1, PMC #2, unknown status

The Agency acknowledges your commitment to submit dissolution data for 24 tablets on the first 12 batches at release or on all batches at release post approval for a period of 12 months, which ever comes first, for each strength. In the submission dated March 18, 2008 to the Agency, you committed to submit this data by 14 months post approval. In addition, you should provide justification, based on the data available after the requested testing period, why a single dissolution specification could not be adopted for all strengths of Venlafaxine hydrochloride Extended Release.

\*\*\* No information/data was found regarding this PMC.

(NO CHANGE) NDA 22104-1, FDAAA #1, fulfilled 10/30/2009 (final report 11/20/2008)

"You are required to conduct a study to investigate dose-dumping in the presence of alcohol by performing dissolution studies for all Venlafaxine hydrochloride Extended Release strengths using the accepted dissolution conditions with the addition of 0%, 5%, 10%, and 20% of ethanol to the dissolution media. The accepted dissolution method is:

Apparatus: USP Apparatus II (Paddle)

Speed: 50 rpm

Media: Water at 37°C

Volume: 900 mL

\*\*\* No dosage information concerning alcohol (ethanol) has been updated.

#### NDA 21450, ZOMIG (ZOLMITRIPTAN) 10/14/2008

(Changed) NDA 21450-5, PREA #1 fulfilled 6/12/2015 (final report 8/14/2014)

Deferred pediatric study under PREA for the acute treatment of migraine in pediatric patients ages 12 to 17 years.

6/12/2015 letter:

"This Prior Approval supplemental new drug application proposes zolmitriptan for the acute treatment of migraine with or without aura in adolescents 12 to 17 years old.

.....

We refer to the deferred pediatric study noted in our S-005 approval letter dated October 14, 2008:

Deferred pediatric study under PREA for the acute treatment of migraine in pediatric patients ages 12 years to 17 years.

We have reviewed your supplemental application (S-008) and conclude that the above requirement was fulfilled."

\*\*\* Sections 1, 2, and 6 were updated based on this study. The approval letter.

#### NDA 22320, 12/8/2008

(Changed) NDA 22320-1, PREA #1, fulfilled Q2 2014, final report 7/12/2012

A multi-center, randomized, placebo-controlled double blind study to evaluate the safety and efficacy of Epiduo Gel administered once daily for the treatment of subjects 9 to 11 years of age with acne vulgaris.

2/1/2013 letter says:

"This "Prior Approval" supplemental new drug application provides for treatment of acne vulgaris in patients 9-11 years of age.

....

We note that you have fulfilled the pediatric study requirement for patients 9 to 11 years of age for this application."

\*\*\* Sections 1 and 6 were updated on 2/1/2013. The letter implies that this change is based on PREA #1.

#### NDA 21567, REYATAZ (ATAZANAVIR SULFATE) 3/25/2008

(Changed) NDA 21567-15, PREA #1, fulfilled 6/2/2014

Deferred pediatric study or studies under PREA for the treatment of HIV - 1 infection in pediatric patients ages greater than or equal to 3 months to 18 years to obtain a minimum of 100 patients followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development.

6/2/2014 letter:

"The new drug application, NDA 206352, provides for the use of a new dosage form, REYATAZ® (atazanavir) oral powder, in combination with other antiretroviral agents for the treatment of HIV-1, in patients over 3 months of age and between 10 kg to < 25 kg.

The Prior Approval supplemental new drug application, sNDA 21567 S-035, updates the shared REYATAZ® (atazanavir) labeling with information on use of the new dosage form, REYATAZ® (atazanavir) oral powder.

....

We note that you have fulfilled the pediatric study requirement (PMR 1244-1) for ages 3 months to 18 years."



\*\*\* On 6/2/2014, sections 1, 2, 6, and 8 were updated based on PREA #1 as the letter says.

#### NDA 50819, ACANYA 10/23/2008

(NO CHANGE) NDA 50819-1, PMC #, fulfilled Q2 2014 final report 8/9/2012

"To conduct a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya Gel. Elements of the said study should include:

- a) Highest frequency of dosing in the proposed label for Acanya Gel
- b) Greatest duration of dosing in the above mentioned labels
- c) Use of to-be-marketed formulation
- d) Maximum total involved surface area to be treated at one time per labeling
- e) Amount applied per square centimeter to be documented
- f) Method of application/site preparation should be documented
- g) Sensitive and validated analytical method to measure active and potential metabolite(s)."

\*\*\* On 02/28/2014, section 12.3 was updated on the absorption of clindamycin. Other than this section, no data/information concerning this PMC has been updated.

#### NDA 22201, FIRMAGON (DEGARELIX ACETATE) 12/24/2008

(Changed) NDA 22201-1, FDAAA #1, fulfilled Q4 2013 final report 6/18/2012

To complete the ongoing extension study FE200486 CS21A entitled "An Open-Label, Multi-Center, Extension Study, Evaluating the Long-Term Safety and Tolerability of Degarelix One Month Dosing Regimen in Patients with Prostate Cancer Requiring Androgen Ablation Therapy".

Actual Primary Completion Date: October 2011

Actual Study Completion Date: December 2011

8/16/2013 letter says:

"This "Prior Approval" supplemental new drug application provides for the addition of data from the extension study FE200486 CS21A to the Adverse Reactions section of the labeling. This is in response to PMR 1273-1 from the December 24, 2008 AP letter. The data was submitted in the Postmarketing Final Report submitted on June 7, 2012."

08/16/2013 label updates

"The safety of FIRMAGON administered monthly was evaluated further in an extension study in 385 patients who completed the above active-controlled trial. Of the 385 patients, 251 patients continued treatment with FIRMAGON and 135 patients crossed over treatment from leuprolide to FIRMAGON. The median treatment duration on the extension study was approximately 43 months (range 1 to 58 months). The most common adverse reactions reported in >10% of the patients were injection site reactions (e.g., pain, erythema, swelling, induration or inflammation), pyrexia, hot flush, weight loss or gain, fatigue, increases in serum levels of hepatic transaminases and GGT. One percent of patients had injection site infections including abscess. Hepatic laboratory abnormalities in the extension study included the following: Grade 1/2 elevations in hepatic transaminases occurred in 47% of patients and Grade 3 elevations occurred in 1% of patients."

\*\*\* The approval letter on 2/25/201 confirms the label changes in section 6.

\*\*\*\* According to the FDA postmarketing drug safety evaluation, adverse event reports of anaphylaxis and cardiovascular disease risk were identified. The Warnings and Precautions section of the labeling for Firmagon was updated in March 2013 to include additional information about hypersensitivity reactions including anaphylaxis. FDA is continuing to evaluate the reports of cardiovascular disease risk to determine if regulatory action is required. This wouldn't affect the coding.

#### NDA 21788, SYNTHETIC CONJUGATED ESTROGENS A, 11/28/2008

★ ★ (terminated) (UNKNOWN) NDA 21788-1, PMC #1, terminated, 1/31/2013 the sponsor requested withdrawal

Duramed commits to design and conduct a Phase IV randomized and placebo-controlled clinical trial to find the lowest effective dose of synthetic conjugated estrogens, A vaginal cream for the indications of (1) treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause and (2) treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

\*\*\* This product was discontinued and there is no label available since the approval date which is 11/28/2008.

#### NDA 22285, KEPPRA XR (LEVETIRACETAM) 9/12/2008

(Changed) NDA 22285-1, PREA #1, final report 1/31/2011 (didn't submit accompanying sNDA/NDA)

"Conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, in comparison to adult patients with epilepsy. The patient population can presently be receiving Keppra. The pharmacokinetic study would include at least 6 pharmacokinetic samples. The comparison group will be an equal number of adult patients studied under the same conditions.

For each group (adolescents and adults), the mean Cmax and AUC must be estimated with a standard error of 20% or less, and this would be the basis for the original sample size calculation. As study data are evaluated, the sample size can be re-assessed if necessary for precise estimation of these pharmacokinetic parameters."

8/1/2014 letter:

"Labeling changes to incorporate new pediatric safety data derived from previously submitted pediatric Postmarketing Requirement studies.

....

We have received your submission dated October 4, 2013, containing the final report for the following postmarketing requirement listed in the September 12, 2008, approval letter.

1476-1 Conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, .....

We have reviewed your submission and conclude that the above requirement was fulfilled."

8/1/2014 label:

"1 INDICATIONS AND USAGE

KEPPRA XR® is indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥12 years of age with epilepsy.

.....

5 WARNINGS AND PRECAUTIONS

5.1 Psychiatric Reactions

Immediate-Release KEPPRA Tablets

A total of 13.3% of adult patients and 37.6% of pediatric patients (4 to 16 years of age) ....."

\*\*\* As stated in the letter, on 8/1/2014 sections 1 and 5 were updated.

\*\*\* According to the FDA postmarketing drug safety evaluation, adverse event reports of medication errors in patients who were switched from Keppra to Keppra XR were identified. This is unrelated to this PMS.

#### NDA 20140, 3/7/2008

(UNKNOWN) NDA 20140-1, PREA #1—unknown, disappeared

You have agreed that the structural identity of the degradation products listed as [...] in the drug product specifications, will be confirmed within six months from the date of approval of the NDA.

\*\*\* This PREA doesn't appear in the FDA PMR/PMC database although it is stated in the approval letter. This may be CMC postmarketing not a reportable PMR/PMC.

#### NDA 22128, 11/25/2008

(NO CHANGE) NDA 22128-S1, PMC #1, fulfilled 9/9/2011 final report 11/30/2010

Conduct an in vivo drug interaction study with maraviroc and the P-glycoprotein substrate digoxin.

02/01/2013 label On section 12:

“In vitro results suggest that maraviroc could inhibit P-gp in the gut. However, maraviroc 513 not significantly affect the pharmacokinetics of digoxin in vivo, indicating maraviroc may not significantly inhibit or induce P-gp clinically.”

\*\*\* Section 12 was updated on 2/1/2013 but this is not considered a major change.

#### BLA 103949, 12/11/2008

(Changed) BLA 103949-5171, FDAAA #1, fulfilled Q4 2014

Completion of the 5-year follow-up observational study of subjects enrolled in Part 2 of the pediatric study P02538, to assess long-term or delayed toxicity including the effect of PegIntron on height and weight and the durability of treatment response. Submit data for at least 50 pediatric subjects completing the 5 year follow-up.

5/21/2015 label changes:

“5.18 Impact on Growth — Pediatric Use Data on the effects of PegIntron plus REBETOL on growth come from an open-label trial in 107 subjects, 3 through 17 years of age, in which weight and height changes are compared to US normative population data. In general, the weight and height gain of pediatric subjects treated with PegIntron plus REBETOL lags behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that PegIntron in combination therapy with REBETOL may induce a growth inhibition that results in reduced adult height in some patients [see Adverse Reactions (6.1)].”

\*\*\* Sections 5, 6, and 8 were updated based on this study: the letter doesn’t confirm the source of evidence, but height and weight long-term follow up data is quite specific to this FDAAA study.

#### NDA 20468, 9/19/2008

(NO CHANGE) NDA 20468-24, PMC #1, fulfilled 7/2/2013 final report 4/13/2011

A controlled clinical trial in pediatric patients with perennial allergic rhinitis to assess the effect of Nasacort AQ (triamcinolone acetonide) Nasal Spray on the HPA axis. Submit a labeling supplement reflecting the results of the clinical trial.

7/2/2013 letter says:

“Prior approval supplemental new drug application NDA 20-468/S-033 proposes to revise the labeling for Nasacort AQ Nasal Spray to include information from a postmarketing growth study.

Prior approval supplemental new drug application NDA 20-468/S-034, proposes to revise the labeling for Nasacort AQ Nasal Spray to include information from a postmarketing HPA axis study.

.....

We have received your submission dated April 13, 2011, containing the final report for the following postmarketing commitment listed in the September 19, 2008, approval letter.

232-1 A controlled clinical trial in pediatric patients with perennial allergic rhinitis to assess the effect of Nasacort AQ (triamcinolone acetonide) Nasal Spray on the HPA axis. Submit a labeling supplement reflecting the results of the clinical trial.

We have also received your submission dated June 22, 2012, containing the final report for the postmarketing commitment to conduct a one year growth study in pediatric patients with Nasacort AQ Nasal Spray.

We have reviewed your submissions and conclude that the above commitments were fulfilled.”

\*\*\* Section 12 was updated on 7/2/2013 which is not a major change.

#### NDA 21588, GLEEVEC (IMATINIB MESYLATE) 12/19/2008

NDA 21588-25, AA#4, fulfilled 2/2/2012 final report 11/31/2011

To complete the clinical trial entitled "Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk of recurrence (SSG XVIII/AIO)" and provide a report and datasets.

1/31/2012 letter:

“This “Prior Approval” supplemental new drug application proposes conversion of accelerated approval to full approval of the indication for adjuvant treatment of adult patients following complete resection of Kit (CD117) positive gastrointestinal stromal tumors (GIST) and provides updated Gleevec prescribing information.

.....  
We have received your submissions dated August 2, 2011 (111-4); November 2, 2011 (111-1), and December 1, 2011 (111-2 and 111-3), containing the final reports for the following postmarketing requirements listed in the December 19, 2008, approval letter.

111-1. To complete the ongoing clinical trial entitled "A single phase III randomized double-blind study of adjuvant imatinib versus placebo in patients who had complete gross resection of their primary gastrointestinal stromal tumor (GIST)" and provide a report and datasets at four years of follow-up for relapse-free survival.

111-2. To complete the ongoing clinical trial entitled "A single phase III randomized double-blind study of adjuvant imatinib versus placebo in patients who had complete gross resection of their primary gastrointestinal stromal tumor (GIST)" and provide a report and datasets at five years of follow-up for relapse-free survival.

111-3. To complete the ongoing clinical trial entitled "A single phase III randomized double-blind study of adjuvant imatinib versus placebo in patients who had complete gross resection of their primary gastrointestinal stromal tumor (GIST)" and provide a report and datasets after collection of 5 years of overall survival data.

111-4. To complete the clinical trial entitled "Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk of recurrence (SSG XVIII/AIO)" and provide a report and datasets.

We have reviewed your submissions and conclude that the above requirements were fulfilled.”

\*\*\* FDA noted that all four studies were fulfilled on 1/31/2012. Sections 1, 6 and 14 were updated on 12 months vs. 36 months treatment.

(UNDETERMINED) NDA 21588-25, AA#1, fulfilled 2/2/2012 final report 11/30/2010

To complete the ongoing clinical trial entitled "A single phase III randomized double-blind study of adjuvant imatinib versus placebo in patients who had complete gross resection of their primary gastrointestinal stromal tumor (GIST)" and provide a report and datasets at four years of follow-up for relapse-free survival.

\*\*\* See comments on AA #4. Regarding studies AA #1, 2, and 3, section 14 was updated which is a minor change. But, it is unclear whether this study has changed any other sections. Therefore it is undetermined.

(UNDETERMINED) NDA 21588-25, AA#2, fulfilled 2/2/2012 final report 11/30/2010

To complete the ongoing clinical trial entitled "A single phase III randomized double-blind study of adjuvant imatinib versus placebo in patients who had complete gross resection of their primary gastrointestinal stromal tumor (GIST)" and provide a report and datasets at five years of follow-up for relapse-free survival.

\*\*\* See comments on AA #4 and AA #1.

(UNDETERMINED) NDA 21588-25, AA#3, fulfilled 2/2/2012 final report 11/31/2011

To complete the ongoing clinical trial entitled "A single phase III randomized double-blind study of adjuvant imatinib versus placebo in patients who had complete gross resection of their primary gastrointestinal stromal tumor (GIST)" and provide a report and datasets after collection of 5 years of overall survival data.

\*\*\* See comments on AA #4 and AA #1.

**NDA 20484, INNOHEP (TINZAPARIN SODIUM) 12/29/2008**

(Changed) NDA 20484-11, FDAAA #1, fulfilled 5/5/2010 final report 3/31/2009

To complete and submit the final report, including electronic datasets, for the clinical trial entitled "Safety Profile of Innohep Versus Subcutaneous Unfractionated Heparin in Elderly Patients with Impaired Renal Function Treated for Acute Deep Vein Thrombosis." Depending on the final results of the trial, you may be required to conduct another clinical trial to evaluate the risk of death with the use of Innohep.

10/7/2010 label update:

“Increased Risk for Death in Elderly Patients with Renal Insufficiency: INNOHEP® may increase the risk for death, compared to UFH, when administered to elderly patients with renal insufficiency. A clinical study compared INNOHEP® (175 IU/kg once daily; N = 269) and UFH (N = 268) in the initial treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in elderly patients with renal insufficiency (i.e., patients aged 70 years or older with estimated creatinine clearance of  $\leq 30$  mL/min or patients aged 75 years or older with estimated creatinine clearance of  $\leq 60$  mL/min). Oral anticoagulants were co-administered beginning on Days 1-3 and study treatment was continued for at least five days until the international normalized ratio (INR) was between 2-3 on two successive days; oral anticoagulants were then continued alone and patients were followed until 90 days after the start of treatment. Overall mortality rates were 6.3% in patients treated with UFH and **11.5%** in patients treated with INNOHEP®. Consider the use of alternatives to INNOHEP® in elderly patients with renal insufficiency.”

--- change from 11.2% to 11.5%

\*\*\* Although the letter doesn't mention the source of evidence, it is likely that this data was from FDAAA #1.

#### NDA 20772, SUCRAID (SACROSIDASE) 11/20/2008

(UNKNOWN) NDA 20772-5, FDAAA #1, fulfilled 5/8/2012 final report 2/28/2012

Conduct a one-year observational study in pediatric and adult patients using the newly manufactured Sucraid to evaluate the incidence of serious adverse reactions, including anaphylaxis and serious allergic reactions.

\*\*\* Labels are not available online.

#### BLA 125057, Humira 2/21/2008, 1/18/2008

(No change) BLA 125057-110, PREA #1 – disappeared Q4 2014

Deferred pediatric study under PREA for the treatment of moderate to severe chronic plaque psoriasis in pediatric patients ages 4 to 17. The pediatric plan is to assess data anticipated from ongoing trials as well as further analysis and assessment of data, including data pertaining to the diagnosis and treatment of psoriasis in the pediatric population, and to establish a study plan that incorporates this new data.

\*\* This PMR disappeared since Q4 2014. FDA says “The study has not been initiated, but does not meet the criterion for delayed. Abbott will submit a pediatric plan proposal to FDA by the target due date specified in the postmarketing requirement” in status description in Q4 2014 data. Then it disappeared.

\*\* I don't find any information on patients for ages 4 to 17 with chronic plaque psoriasis.

(UNDETERMINED) BLA 125057-110, PMC #4 fulfilled Q2 2011

Provide information on effects of discontinuation of Humira followed by a second course of Humira in patients treated successfully with the drug. This information will be obtained from a minimum of 120 evaluable subjects currently participating in Study M03-658 "A Multicenter Open-Label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects who Completed a Preceding Psoriasis Clinical Study with Adalimumab". Subjects meeting response criteria will be discontinued from treatment and reinitiated Humira therapy upon relapse to evaluate whether additional use of Humira will impact safety and efficacy. Study Report Submission: April 2010 If the information from ongoing clinical trials is insufficient, a new trial will be conducted to assess effects of discontinuation followed by a second course of Humira in patients treated successfully with the drug.

(UNDETERMINED) BLA 125057-110 PMC #3 fulfilled Q2 2011

Submit the final study report for trial M03-658, "A Multicenter Open-Label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects who Completed a Preceding Psoriasis Clinical Study with Adalimumab".

(Changed) BLA 125057-114, PMC #2

Conduct a compassionate use study in patients 2 to 4 years of age with moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) to collect pharmacokinetic data in 6 to 20 patients and to collect safety data in 30 patients according to the safety assessment specified in postmarketing commitment number 1.

9/30/2014 letter:

“This Prior Approval supplemental biologics application provides for the treatment of Polyarticular Juvenile Idiopathic Arthritis (pJIA) in patients 2 to less than 4 years of age.

...

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

This submission also contains the final report for the following postmarketing commitment listed in the February 21, 2008, approval letter for BLA 125057/S-114.

Conduct a compassionate use study in patients 2 to 4 years of age with moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) to collect pharmacokinetic data in 6 to 20 patients and to collect safety data in 30 patients....

We have reviewed your submission and conclude that the above commitment was fulfilled.”

\*\* The letter confirms it.

### **G.3 Black Box Warnings**

(no PMS associated) BLA 125057, Humira , TNF blocker

There was a black box warning for a class of TNF blockers. The drugs in this class include Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol) and Simponi (golimumab). A black box warning on about the increased risk of lymphomas and other cancers associated with the use of TNF blockers (malignancies).

<http://wayback.archive-it.org/7993/20161022203927/http://www.fda.gov/Drugs/DrugSafety/ucm250913.htm>

FDA explains that the warnings and safety communication were based on data from the Adverse Event Reporting System (AERS) database (de-duplicated), the literature, and the HSTCL Cancer Survivors' Network in association with the following agents (mutually exclusive): Infliximab (20), etanercept (1), adalimumab (2), infliximab/adalimumab (5), certolizumab (0), golimumab (0), azathioprine (12), and mercaptopurine (3). FDA didn't mention about the postmarketing studies associated with Humira.

(no PMS associated) BLA 125160, Cimzia, TNF blocker

See description above for Humira.

(no PMS associated) NDA 22291, PROMACTA (ELTROMBOPAG)

In 2012, a black box warning was added: “PROMACTA, in combination with interferon and ribavirin in patients with chronic hepatitis C, may increase the risk of hepatic decompensation.”

Among fulfilled postmarketing studies (TRA 102537—NCT00370331, TRA108057—NCT00424177, TRA105325—NCT00351468), there was no trial that had ribavirin as an intervention drug.

(no PMS associated) NDA 22304, Nucynta – IR opioid

In 2016, there was a warning on opioid drugs about the serious risks of misuse, abuse, addiction, overdose and death:

NUCYNTA tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)

- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)
- Accidental ingestion of NUCYNTA tablets, especially by children, can result in a fatal overdose of tapentadol. (5.2)
- Prolonged use of NUCYNTA tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation (5.4), (7).

FDA investigated several safety issues associated with the class of opioid pain medicines:

Serotonin syndrome, Adrenal insufficiency, and Androgen deficiency based on FAERS and medical literature (<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm>)

Also, all postmarketing studies associated with Nucynta were PREA studies.

IR opioids include immediate release morphine, hydromorphone, hydrocodone and combination products, including Opana IR and Nucynta.

#### List of ER/LA opioid

1	Avinza	Morphine sulfate extended-release capsules	Pfizer
2	Butrans	Buprenorphine transdermal system	Purdue Pharma
3	Dolophine	Methadone hydrochloride tablets	Roxane
4	Duragesic	Fentanyl transdermal system	Janssen Pharmaceuticals
5	**Embeda	Morphine sulfate and naltrexone extended-release capsules	Pfizer
6	Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt
7	Kadian	Morphine sulfate extended-release capsules	Actavis
8	MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma
9	Nucynta ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals
10	Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals
11	OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma
12	*Palladone	Hydromorphone hydrochloride extended-release capsules	Purdue pharm

\*No longer being marketed, but is still approved.

\*\*Not currently available or marketed due to a voluntary recall, but is still approved.

(3 unrelated, 1 undetermined) NDA 22090, Eovist

A black box warning was added: "For patients at risk for chronically reduced renal function (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing."

Among 4 PMR/PMCs, one of them was released, and two of them were PREA studies. The other study (PMC) is a crossover study to evaluate the possible influence of Erythromycin as an example of an inhibitor of the organic anion transporting peptide on the hepatocyte uptake of Eovist in liver MR imaging in healthy subjects. It is unclear if this BBW was based on the data from this PMC.

(no PMS associated) NDA 22195, 22207 MORPHINE SULFATE, Opioid

In 2016, BBW was added:

“WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS See full prescribing information for complete boxed warning.

- Ensure accuracy when prescribing, dispensing, and administering Morphine Sulfate Oral Solution. Dosing errors due to confusion between mg and mL, and other morphine solutions of different concentrations can result in accidental overdose and death. (2.1, 5.1)

- Morphine Sulfate Oral Solution exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient’s risk before prescribing and monitor regularly for these behaviors and conditions. (5.2)

- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)

- Accidental ingestion of Morphine Sulfate Oral Solution, especially by children, can result in a fatal overdose of morphine. (5.3)

- Prolonged use of Morphine Sulfate Oral Solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)”

This was a class wide action. Two PMR/PMCs associated with this morphine sulfate were:

A minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%: a. 10-hydroxymorphine b. pseudomorphine, and c. morphine-N-oxide

D eferred pediatric study under PREA for the treatment moderate to severe acute and chronic pain where an opioid analgesic is appropriate in pediatric patients ages 0 to 17.

These warnings are not associated with these two studies.

(undetermined) NDA 21775, Entereg, opioid antagonist to accelerate time for gastrointestinal recovery

A BBW was added in 2013:

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE: FOR SHORT-TERM HOSPITAL USE ONLY

There was a greater incidence of myocardial infarction in alvimopan-treated patients compared to placebo-treated patients in a 12-month clinical trial, although a causal relationship has not been established. In short-term trials with ENTEREG®, no increased risk of myocardial infarction was observed.

A FDAAA study “A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management or postoperative ileus in patients undergoing radical cystectomy” might have produced evidence for this warning, but it is unclear. It is likely that this FDAAA is registered as NCT00708201 on clinicaltrials.gov. In warning section (5.1), the description of the study fits the study NCT00708201 except for the sample size. It is unclear.

(no PMS associated) NDA 22148, Cymbalta

A BBW was removed in October 2014.

BOXED WARNING: Suicidal Thoughts and Behaviors

The following statement was removed:

Cymbalta is not approved for use in pediatric patients



1 PREA and 1 FDAAA were unfulfilled. 1 PMC is a randomized, double-blind, placebo-controlled study of Cymbalta at lower doses of 20 - 30 mg per day in the management of fibromyalgia. It is unlikely that this BBW was removed based on this PMC.

#### (no PMS related) NDA 21926, Treximet

A BBW was added on May 2016:

TREXIMET is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4) Warnings and Precautions (5.1)].

2 PREA studies were unrelated. 1 FDAAA might have produced evidence, but it is unlikely because the FDAAA is a randomized, double-blind, active comparator clinical trial of Treximet in adults with episodic migraine dosed with either Treximet, naproxen sodium 500 mg, or sumatriptan 85 mg to further assess the hypertensive effects of Treximet relative to each of its two active ingredients. CABG surgery was not related to this FDAAA.

#### (undetermined) BLA 103949, PEGINTRON PEGINTERFERON ALFA-2B

A box was added: “Alpha interferons, including PegIntron, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping PegIntron therapy [see Warnings and Precautions (5) and Adverse Reactions (6.1)]. Use with Ribavirin Ribavirin may cause birth defects and death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. [See ribavirin labeling.]” in 2009. There was no boxed warning at the time of approval in 2008 – there were highlighted warnings though. The boxed warning is very similar to the highlighted warning at the time of 2008.

FDAAA is a completion of the 5-year follow-up observational study of subjects enrolled in Part 2 of the pediatric study P02538, to assess long-term or delayed toxicity including the effect of PegIntron on height and weight and the durability of treatment response. Submit data for at least 50 pediatric subjects completing the 5 year follow-up. It is unclear whether this FDAAA had provided evidence for the box warnings.

#### (undetermined) BLA 103792 HERCEPTIN/TRASTUZUMAB

Embryo-Fetal Toxicity (oct 2010) was added as BBW. The label says “In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.”

This drug had 4 fulfilled PMS. 1 FDAAA and 3 PMCs. One PMC was about QT interval. And the FDAAA study was DDI study. Another PMC was about cardiac safety study. And lastly, a PMC was updated safety reports. It is unclear whether the report came from the study or not.

PMC #1 To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of trastuzumab treatment in Study BO16348 (HERA) in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

PMC #2 To provide updated safety information of the observation and 1-year trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on

an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

## G.4 EXCEPTIONS

For some cases, a PMS developed into different PM studies. For example, NDA 22029 (Salonpas) had a PREA study:

Deferred pediatric study under PREA for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains in pediatric patients ages 3 to 17.

On 11/5/2012, FDA said:

“We are waiving the pediatric study requirement for ages 0 months to 2 years and 11 months due to safety concerns related to salicylate exposure and Reye’s syndrome; we are waiving trials in children aged 3 to 5 years 11 months of age because sprains and strains only very infrequently occur in this age group, therefore the drug does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of pediatric patients. We are deferring submission of pediatric studies for ages 6 years to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.”

On the FDA letter 03/29/2013:

“We remind you of your pediatric study requirements, as described in our February 20, 2008, approval letter:

1073-1 Deferred pediatric study under PREA for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains in pediatric patients ages 3 to 17.

The pediatric study requirement for ages 0 months to 2 years and 11 months was waived due to safety concerns related to salicylate exposure and Reye’s syndrome. Additionally, as stated in our November 5, 2012, supplement approval letter, pediatric studies in children aged 3 to 5 years 11 months of age were waived because sprains and strains only very infrequently occur in this age group, therefore Salonpas does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of pediatric patients.

We have reviewed your submission dated May 30, 2012 and have determined that you have fulfilled the above requirement for study of Salonpas in patients ages 13 to 17 years and 11 months. In addition, based on the lack of efficacy found in the 13-17 year age group, we are waiving the requirement for studies in patients ages 3 years to 12 years and 11 months because there is evidence strongly suggesting that the drug product would be ineffective and/or unsafe in this pediatric group. Therefore, you are released from this portion of the postmarketing requirement.

Because you have fulfilled the requirement for study of Salonpas in one age group and are waived from the remainder, this postmarketing requirement will be administratively separated into two postmarketing requirements as follows:

1073-2 Deferred pediatric study under PREA for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains in pediatric patients ages 3 to 12 years and 11 months. This requirement is released.

1073-3 Deferred pediatric study under PREA for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains in pediatric patients ages 13 to 17 years and 11 months. This requirement is fulfilled.”

## **G.5 EXCLUDED FROM SAMPLE**

\*\*\* these PMCs were agreed in 2006, but this NDA was approved in 2008. Not in the system. It is unclear whether these are reportable commitments.

NDA 22029, Salonpas (Menthol; Methyl Salicylate) 2/20/2008

NDA 22029-1, PMC # not in the dataset – agreed in 2006

"Develop a dissolution method to replace the originally-proposed in vitro release method. Submit the final method and supporting data to the FDA within six (6) months of the date of this letter."

NDA 22029-1, PMC # not in the dataset – agreed in 2006

Evaluate the loss of drug substance during the validation campaign for commercial scale production and make appropriate adjustments to the percent overage of drug substances as necessary. Evaluate an additional five lots and make further adjustments as indicated. Submit a report detailing this work to the FDA within six (6) months of the date of this letter.

## Appendix H for paper 2: Label changes (2009-2017) and PMR/PMCs

This analysis aims to look at how likely PMR/PMCs are associated with important labeling revisions (BBW, indications, dosage, contraindications, and warnings). Out of 2008 drug approval sample, I took a sub-sample of drugs that were approved before 2008 and did not have PMS during 2008-2016. A total of 56 drugs were included: 39 drugs had postmarketing studies before 2008 and 17 drugs had no postmarketing studies before 2008.

From this sample of drugs, I obtained all label changes between 2008 and 2017 and coded whether a labeling revision had changes on BBW, Indications, Dosage, Contraindications, and Warnings. After excluding 16 labeling revisions without further information, a total of 333 labeling revisions were included in this sub-sample: 232 labeling revisions were associated with 39 drugs (70%) with previous postmarketing studies and 101 labeling revisions were associated with 17 drugs (30%) without previous studies. For sampling criteria, see Figure 2-15.

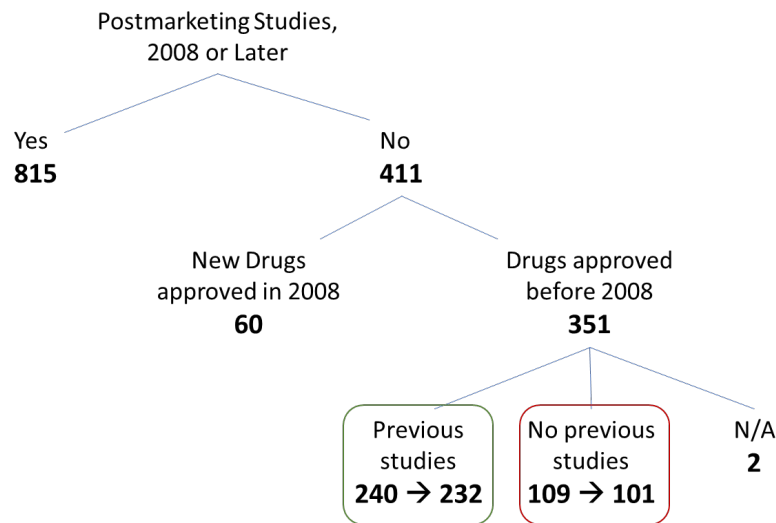


Figure H-15. Label change sample, 333 out of total 1,226 label revision approvals

Notes: the sample includes label changes of drugs approved before 2008 with no previous postmarketing studies and no studies at the approval in 2008 (109) and label changes of drugs approved before 2008 with previous studies but without studies in 2008 (240). After excluding 16 labeling revisions, a total of 333 were included in the analysis: 232 with previous postmarketing studies and 101 without previous studies.

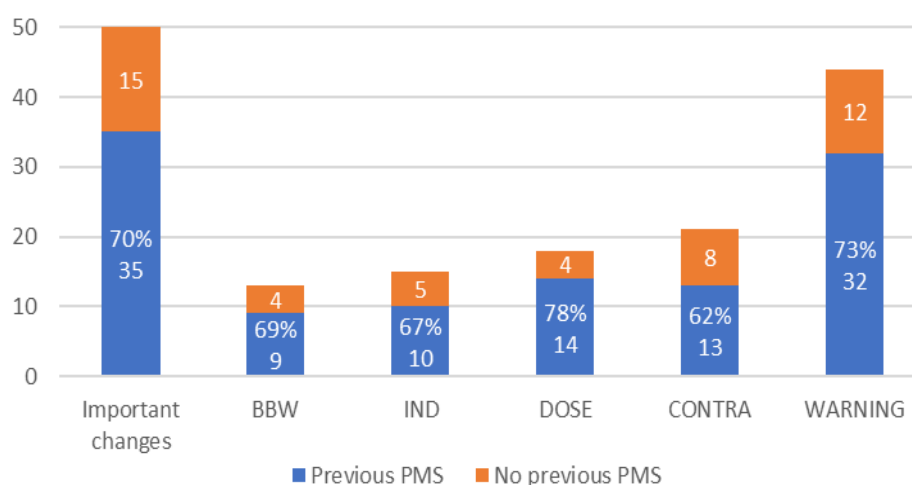
Table 2-32 shows that 70% of drugs (35 out of 50) with label changes had labeling revisions when they had postmarketing studies. There was no difference in drugs with PMR/PMCs and without studies in terms of the percentage of important label changes of all label changes: 90% for drugs with PMR/PMCs (35 out of 39) and 88% for drugs without them (15 out of 17). The percentage was higher in dosage and warning changes compared to revisions in BBW, indications, and contraindications. (Figure 2-16)

**Table H-32. Drugs with label changes, with no further PMS since 2008, by previous PMS**

	Drugs	Important change*	BBW	IND	DOSE	CONTRA	WARNING
Previous PMS	39	35	9	10	14	13	32
No previous PMS	17	15	4	5	4	8	12
Total	56	50	13	15	18	21	44

Notes:

1. The sample includes drug-approvals before 2008 and no postmarketing studies in 2008 or later.
2. \* Important label change counts drug-approvals with any of BBW, Indication, Dose, Contraindication, and Warning changed.



**Figure H-16. Drugs with label changes, by previous PMS vs. without previous PMS**

Notes:

1. The sample includes drugs approved before 2008 (1997-2007) and no postmarketing studies in 2008 or later until 2016. The sample size is 56 drugs (39 drugs had previous PMS and 17 drugs had no PMS previously). Among 56 drugs, 50 drugs had label changes.
2. The percentage of drugs with previous PMS of all drugs with label changes. For example, among 13 drugs with labeling revisions, 9 had BBW changes (69%, the blue bar in BBW).
3. Label change is a change in the following sections: BBW, indications, Dosage, Contraindication, and Warnings. Any of these changes is accounted label change.
4. See Table 2-32 for data.

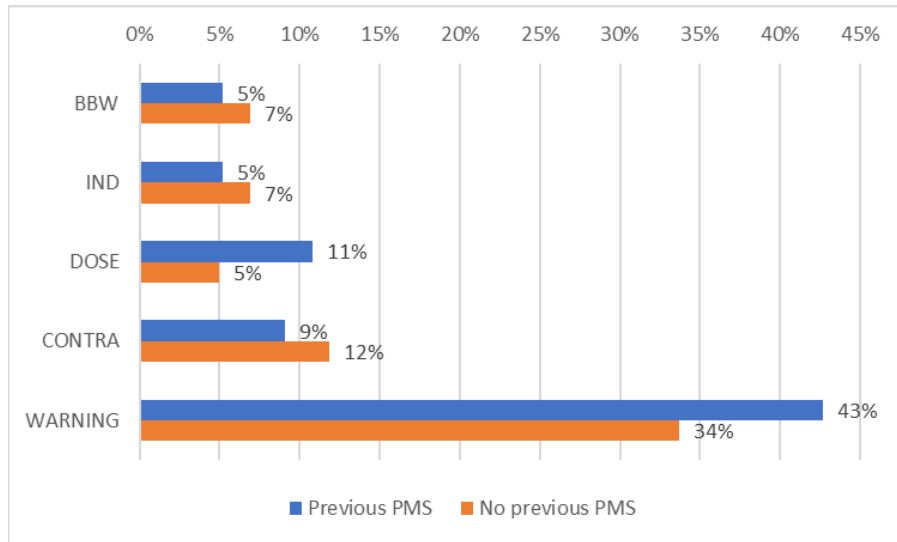
Figure 2-17 and Table 2-33 show how many important label changes were made in each section with PMS and without PMS. Among all 232 label changes for the drugs with PMS, 126 labeling revisions were made in important sections of the labels (54%). Forty four out of 101 labeling revisions were important changes for the drugs without PMS (44%). Out of a total of 333 label changes, 6% (19) had BBW, 6% (19) had indication changes, 9% (30) had dosage changes, 10% (33) had contraindications, and 40% (133) had warnings.

**Table H-33. Label changes, by previous PMS or without previous PMS**

	BBW	IND	DOSE	CONTRA	WARNING	total labels changed in 5 sections	Other sections	Total labels changed
Previous PMS	12	12	25	21	99	126 (54%)	106	232
No PMS	7	7	5	12	34	44 (44%)	57	101
Total	19	19	30	33	133	170	163	333

Notes: The sum of BBW, indication, dosage, contraindication, and warning changes is not equal to the total number of labels changed in those five sections. It is because one labeling revision supplemental has changes in multiple sections of label.

Figure 2-17 shows that the percentage of label changes in dosage and warnings sections out of all label changes is higher in drugs with PMS compared to ones without PMS. In BBW, indications, and contraindication sections, there was no difference between drugs with PMS and drugs without them in terms of the percentage of label changes out of all label changes.



**Figure H-17. Label changes, by previous PMS or without previous PMS**

**Notes:**

1. The percentage indicates the percentage of labeling revisions for the drugs with previous PMS or without previous PMS. For example, among 232 label changes for the drugs with previous PMS, 12 had BBW revisions (5%, the blue bar in BBW).
2. See Table 2-21 in Appendix D and Figure 2-12 in Appendix E for the same analysis for drugs. This figure depicts labeling revisions not drugs.
3. See Table 2-29 for data.



### **3.0 Study 3: The effect of postmarketing studies on drug approval process**

#### **Abstract**

The importance of postmarketing studies in drug regulation has increased in the United States. With a paradigm shift from an approval-oriented approach to a lifecycle management approach and increasing expedited approvals, postmarketing studies may play a role on the drug approval process by increasing confidence that problems with a drug will be identified relatively quickly after approval. This paper addresses whether and how the availability of postmarketing study options affects the drug approval process by examining qualitative data from Food and Drug Administration (FDA) drug advisory committee meeting transcripts (115 meetings during 1985-1989 and 2012-2016) and interviews. I found a few statements by advisory committee members indicating that the prospect of postmarketing studies made them more likely to support approval of a specific drug. However, these statements were found in only 3.5% of the transcripts. Interviews with 12 participants in the drug approval process revealed quite divergent views about the influence of the availability of PM studies. The supporting evidence for a role of postmarketing studies on the approval process may be greater than the transcripts reveal, but, if so, it is not through discussions at the advisory committee meetings.

### 3.1 Introduction

Passage of the 21st Century Cures Act in 2016 allowed the Food and Drug Administration (FDA) to expand the types of evidence used to assess the safety and efficacy of new drugs. Major changes were (1) the addition of biomarkers, surrogate measures, and other measures that it did not involve clinical endpoints, (2) use of patient experience information in regulatory decision making, and (3) use of real-world observational data rather than randomized clinical trial data to support new indications for existing drugs. Its advocates welcomed these changes as tools to speed drug development. The opponents warn this is “a solution to a problem that mostly does not exist” because the idea that FDA standards for drug approval are too demanding is a fundamental misconception (Kesselheim and Avorn, 2017).<sup>156</sup>

This policy debate is not new. Since the drug lag debate in the 1970s, FDA’s drug approval policies have been viewed as trade-offs between faster approval with laxer rules and stricter pre-approval evidence requirements with slower approval. The demand for postmarketing studies<sup>157</sup> and surveillance has been rising. Although the postmarketing studies have been increasing for the past several decades, the possible effects of this change on the drug approval process is little known. One might expect that having postmarketing studies plays a role in trade-offs between approving drugs faster with postmarketing studies and delaying approvals.

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<sup>156</sup> “The FDA is currently developing guidance on the various uses of so-called real-world evidence, which is often drawn from health care claims data.....The bill also creates a new “regenerative advanced therapy” designation, which allows a wide variety of products to undergo expedited development and review, including “cell therapy, therapeutic tissue engineering products, [and] human cell and tissue products.”....The new law also allows the FDA to approve new indications for existing drugs based on data summaries alone.” (Kesselheim and Avorn, 2017)

<sup>157</sup> FDAAA makes a distinction between “study” and “clinical trial.” Previous laws, regulations, and practice generally used the terms studies and trials interchangeably. For example, section 506B of the Act (21 U.S.C. 356b) uses “studies” to describe the postmarketing commitments (PMCs) that must be reported annually, including clinical trials. Hereinafter, I use the term “study” for both clinical trials and non-clinical-trial studies in this document unless the distinction is necessary. Thus, postmarketing studies (PMS) include postmarketing requirements (PMR) and postmarketing commitments (PMC) in trial, observational, and non-clinical settings.

In one crucial sense, the effect of greater use of postmarketing studies on drug approval is obvious. In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), which allowed the FDA to offer “accelerated approval” for important new drugs which had not yet met the agency’s usual evidentiary standard. In return, the sponsors of those drugs were required to carry out postmarketing studies to confirm their efficacy. This paper investigates—within the framework of that compromise—whether, how, and to what extent the availability of postmarketing study options affects the drug approval process.

Our approach here includes an analysis of FDA advisory committee meeting transcripts to see if they provide evidence about how that availability affects the committee members’ discussions on drug approval issues. I also interviewed stakeholders to learn how they perceived the role of postmarketing studies on drug approval process.

Findings from this analysis are especially germane because: (1) expedited approvals, surrogate markers-based, and single pivotal trial- based approvals have continued to increase (Kesselheim et al., 2015); and (2) a lifecycle approach enables FDA to approve drugs with less robust evidence under the assumption that more studies will be carried out. In this context, examining the effect of postmarketing studies on the drug approval process sheds light on the role of postmarketing studies in this era of drug lifecycle management.

### 3.2 Background and Literature

Postmarketing study (PMS) is a term used to describe all research activities after the approval of a new drug application (NDA) or biologic license application (BLA)<sup>158</sup> by the FDA. A postmarketing requirement (PMR) is a study that the FDA mandates as a condition for approval as defined in section 901 of the 2007 FDAAA<sup>159</sup>. On the other hand, a study that is not required by statute might be conducted because a sponsor and the FDA agree, in writing, that such study should be conducted. This is a postmarketing commitment (PMC). See Table 3-1 for types and legal statutes of PMRs and PMCs.

**Table 3-1. Types of Postmarketing Studies and Statutes**

	Requirement (PMR)	Commitment (PMC)
Laws/Rules	<ul style="list-style-type: none"> <li>• Animal Efficacy: 1999 Animal Rules<sup>160</sup></li> <li>• Accelerated Approval: 1992 Accelerated Rules<sup>161</sup></li> <li>• Pediatric Studies: 2003 PREA<sup>162</sup></li> <li>• Safety studies<sup>163</sup>; 2007 FDAAA<sup>164</sup></li> </ul>	1997 FDAMA <sup>165</sup> (Agreed-upon postmarketing studies that do not meet the statutory criteria for PMRs)
Enforcement	Charges under section 505 of the Act Misbranding charges (section 502(z)) Civil monetary penalties (section 303(f))	No enforcement

<sup>158</sup> Conventional drugs are chemically synthesized, and biologics are manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are large, complex molecules or mixtures of molecules. Hereinafter, “drugs” refer to both conventional drugs and biologics regulated by CDER. CBER biologics are not included.

<sup>159</sup> Section 901 of the 2007 FDAAA created section 505(o) of the FD&C Act that states that the FDA can mandate PMRs in certain situations such as to confirm clinical benefit when a drug has been given “accelerated approval,” to assess risk associated with the drug, or to examine pediatric populations.

<sup>160</sup> 21 CFR 314.610(b)(1), Subpart I (drugs); 21 CFR 601.91(b)(1), Subpart H (biologics)

<sup>161</sup> 21 CFR 314.510, Subpart H (drugs); 21 CFR 601.41, Subpart E (biologics)

<sup>162</sup> 21 CFR 314.55(b) (drugs); 21 CFR 601.27(b) (biologics)

<sup>163</sup> Section 505(o) of the Act states that postmarketing studies and clinical trials may be required for any or all of three purposes related to risk:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

<sup>164</sup> Section 505(o)(3) of the FDCA

<sup>165</sup> 21 CFR 312.85

Animal efficacy studies are required for a drug that was approved on the basis of animal efficacy data because human efficacy trials are not ethical or feasible.<sup>166</sup> Confirmatory studies for accelerated approval are required to verify and describe the predicted effect or other clinical benefit for drugs approved in accordance with the accelerated approval provisions in section 506(c)(2)(A) of the FD&C Act.<sup>167</sup> Under the Pediatric Research and Equity Act (PREA), pediatric studies are required to study certain new drugs for pediatric populations, when these drugs are not adequately labeled for children. And, FDAAA safety studies are required “to assess a known serious risk, assess signals of serious risk, or identify an unexpected serious risk (when available data indicates the potential for a serious risk) related to the use of a drug product (section 505(o)(3) of the Food, Drug and Cosmetic Act (FD&C Act), as added by the FDAAA of 2007).”<sup>168</sup>

### **3.2.1 Drug lag and policy changes**

Since the passage of the 1962 Kefauver-Harris Amendment, debates about FDA drug approval policies have focused on the potential conflicts between facilitating access to new drugs and ensuring that the drugs were safe and effective. This tension is built into the mission of the FDA. Some critics have argued that the system puts too much emphasis on tight preapproval requirements and too little on examining what happened with the drugs once they reached much greater numbers of users in the marketplace (Institute of Medicine (IOM), 2006; Avorn, 2004).

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<sup>166</sup> 21 CFR 314.610(b)(1) and 601.91(b)(1) “PMRs for drug products approved under the animal efficacy rule can be conducted only when the product is used for its indication and when an exigency (or event/need) arises. In the absence of a public health emergency, these studies/clinical trials will remain pending indefinitely.” Guidance for Industry.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077374.pdf>

<sup>167</sup> 21 CFR 314.510 and 601.41 Guidance for Industry.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077374.pdf>

<sup>168</sup> <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077374.pdf>

Requiring strong evidence of safety and efficacy of a drug before its approval could prevent harmful or ineffective drugs from being marketed, and thus save lives and costs. But, it could also delay access to drugs for patients who may benefit from a potentially life-saving drug as well as limit the firms' resources to develop new drugs.

During the 1970s, drug regulation debates centered on the “drug lag” issue. The original focus was the delay between approval in the US and approval in foreign countries such as the UK. Critics of the FDA argued that the 1962 Amendments to the Federal Food, Drug, and Cosmetic (FD&C) Act reduced the incentive of firms to develop innovative drugs and limited treatment options for patients who desperately needed medicines (See Wardell; Peltzman). Some drug policy scholars and policymakers advocated that the regulatory system would work better if the FDA placed more emphasis on examining the safety and efficacy of drugs after marketing and on reducing the barriers to the approval itself (Wardell and Lasagna, 1975; Wardell, 1979; Viscusi et al., 2005; Gottlieb, 2016<sup>169</sup>; Becker, 2002).

Another source of delay in drug approval is the time required for the FDA's review of new applications. In this context, critics claimed that the agency's review process took too long (Hutt and Merrill, 1980). The median FDA review time for New Molecular Entities (NME) submitted in 1978 was 30.8 months (Carpenter, 2004).<sup>170</sup> Note that most of the pre-marketing time is spent on drug development, conducting clinical trials. Thus, pre-approval evidence requirements are also important for delays as much as the review time once a drug application is filed.

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<sup>169</sup> “Expediting the development of these novel and transformative technologies like gene- and cell-based therapies doesn't necessarily mean lowering the standard for approval, as I believe other countries have done. But it does mean having a framework that's crafted to deal with the unique hypothetical risks that these products pose. It means shifting much more of the emphasis on active surveillance as opposed to FDA's historically more binary approach to regulation, that transfers most of the responsibility to the pre-market review process.” Scott Gottlieb (2016), <https://www.forbes.com/sites/scottgottlieb/2016/01/12/fda-needs-to-change-how-it-regulates-novel-technologies/#2636756c191e>

<sup>170</sup> After PDUFA, the average review time for NMEs during 2008-2009 was 13 months.

To some degree, these critiques of drug lag have contributed to the changes in FDA policy adopted since the 1990s. Scholars also identified other factors<sup>171</sup> that might have influenced FDA policy. One of them is disease-specific lobbying by patient advocacy groups—i.e. AIDS activists, American Cancer Society, and National Cancer Institute (See Hutt; Temin; Carpenter). It is accepted that the patient advocacy intensified drug lag controversy. And, the critiques of drug lag based on scientific and economic evidence fortified the case for regulatory change.

Another factor that influenced the FDA policy is a lifecycle management<sup>172</sup>. A drug regulation paradigm was shifted from an approval-oriented approach to a lifecycle approach and this paradigm change was reflected in the Institute of Medicine (IOM)’s recommendations to the FDA in 2006. The rationale for the lifecycle approach is that our understanding of benefits and risks of a drug changes over a drug’s lifecycle and our attention to them should be sustained throughout the lifecycle (FDA, 2004). This paradigm shift not only emphasizes the importance of postmarketing studies, but also enables the FDA to expedite approval (Pease et al., 2017).

Given these critiques and changes in the policy environment, measures have been taken to speed drug approval: among the measures taken are accelerated approval, priority review, breakthrough therapy, and fast track<sup>173</sup>. For instance, accelerated approval, officially established

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<sup>171</sup> Other factors include industry influence, i.e. captured regulatory agency (Quirk; Abraham; Carpenter; Olson), and presidential preferences, i.e. anti-regulatory Reagan and Bush administration (Ceccoli).

<sup>172</sup> Lifecycle evaluation “emphasizes the importance of continuing to collect data on the effectiveness and safety of medical products after approval for a given indication over the entire span of their use by patients. And it involves ongoing review of the published literature, adverse event reporting systems, manufacturer safety reports, and drug use databases. Specific methods or intensity of postapproval evaluation can vary based on what is known about the benefits and risks of each drug. It contrasts with historical concept of regulators as completing product evaluation exclusively (or near exclusively) by the time of initial regulatory approval.” (Pease et al., 2017)

<sup>173</sup> Orphan drug designation qualifies the sponsor for development incentives of the orphan drug, including tax credits for qualified clinical testing, patent exclusivity, and fee waiver for PDUFA. Orphan drugs do not automatically qualify for expedited approval.

in 1992, is an approval path that allows drugs to be approved based on surrogate markers and other programs are status designation that are given to special circumstances<sup>174</sup>.

In addition, the Prescription Drug User Fee Act (PDUFA) was enacted in 1992 to help the FDA shorten review times.<sup>175</sup> Under the PDUFA, FDA agreed to specific goals for drug review time and created priority review. A priority review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

Through the Food and Drug Administration Modernization Act (FDAMA) of 1997, Congress concurred with the view of the Advisory Committee, chartered to examine the FDA's mission and responsibilities by the secretary of HHS, that FDA's mission is not only to prevent harmful products, but also to approve new drugs in a timely manner.<sup>176</sup> FDAMA further expanded

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<sup>174</sup> 506(c) of the FD&C Act defines that accelerated approval is for "a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." Here, a serious condition or disease is defined as: ". . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." (21 CFR 312.300(b)(1))

<sup>175</sup> "It (PDUFA) has been a key to ending major problems with unpredictable and slow review and approval of new drug applications. It has provided funds to eliminate or even reverse the so-called "drug lag" attributed to inadequate staff and computer resources. Americans now get access to more new medicines faster than patients in other countries, while prior to PDUFA, American patients waited for FDA to act long after new drugs were available in Europe." FDA acknowledged PDUFA as a tool to reduce the drug lag. Source: FDA. White Paper, "Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications." (No publication date, but it seems to have been published in 2005 or 2006)

<sup>176</sup> "In formulating a statement of purpose and program goals, the committee found that--

\* \* \* the agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products. This is especially true for people with life-threatening illnesses and for diseases for which alternative therapies have not been approved." REP. No. 105-43, at 8 (1997). See Parver (1999).



expedited approval process by adding “fast track.”<sup>177</sup> FDAMA's fast track program allows for the rolling review of applications and provides an additional basis for approving drugs fast. The Orphan Drug Act of 1983 is also regarded as an effective policy to reduce the drug lag in rare diseases<sup>178 179</sup> in the US (Grabowski and Wang, 2006).<sup>180</sup> In addition, in 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed. FDASIA Section 902 provides for a new expedited approval path - breakthrough therapy that may present substantial improvement over existing therapies.

### 3.2.2 Increasing demand for postmarketing studies

Increases in expedited approvals and the introduction of PDUFA, in turn, made postmarketing studies and surveillance more critical. Consumer groups and scholars “became concerned that the increased pace of drug approvals had unintentionally led to a neglect of—or at least insufficient attention to—safety considerations, resulting in what was seen as a greater rate

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<sup>177</sup> “It allowed for the possibility of drug approval based on a single phase II trial without traditional phase III trials. The rationale for moving to a two-phase process was that desperately ill patients and their physicians were generally willing to accept greater risks and uncertainty. The regulations allowed the FDA to seek agreement from the drug sponsor to conduct postapproval (phase IV) studies to collect additional risk and benefit information” (Kesselheim and Darrow, 2015)

<sup>178</sup> According to 21CFR Part 316, the term “rare disease or condition” means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.

<sup>179</sup> The costs of obtaining FDA approval were the same regardless of whether a drug under development was intended to treat an illness afflicting small number of patients or large target population, FDA regulation has had especially negative consequences on drugs intended for small markets. To counter that disincentive, the Orphan Drug Act (ODA) was enacted in an effort to reduce drug loss in the area of rare diseases. The ODA gave tax breaks, subsidies, and (most importantly) seven years of market exclusivity to sponsors of drugs for rare diseases. (Tabarrok, 2001 winter, *The Blessed Monopolies, Regulation*, Cato Institute)

<sup>180</sup> Grabowski and Wang’s country-level analyses for 1993–2003 indicate that U.S. firms overtook their European counterparts in innovative performance for the introduction of first-in-class, biotech, and orphan products.

of drug withdrawals.” (IOM, 2006) FDA’s performance in approving drugs and monitoring their safety after approval has been questioned as drug safety concerns continue to emerge (Darrow et al., 2014).<sup>181</sup> Scholars found that the expedited approvals led to more safety events after approval (Wallach et al., 2018; Frank et al., 2014; Downing et al., 2017).

Moreover, since the 2000s, spurred by safety problems with Vioxx and Avandia, considerable public debate has centered on drug safety (IOM, 2007; IOM, 2012). The numbers of serious events reported in the FDA Adverse Event Reporting System (FAERS) have been increasing, along with the percentage of serious outcomes of those safety reports. For instance, the number of serious events reported in 2006 was 230,389 (deaths: 37,373) and, in 2018, the number increased to 1,109,481 (deaths: 197,060) which is five times as many as 2006 safety events<sup>182</sup> (See Table 3-5 in Appendix I for more details on drug-related safety events).

However, spontaneous reports (FAERS data) do not provide evidence for causal relationships between drugs and events, and FAERS is less useful for “the events with high background rates, worsening of pre-existing disease, comparative incidence rates, comparing drugs in the same class, adverse events that could also be manifestations of the disease for which the drug is indicated, etc.” (Muñoz, 2016). All of these limitations prevent FAERS from providing

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<sup>181</sup> The risk of “truncated premarket review” became clear when FDA suspended ponatinib, a treatment for leukemia, in October 2013 (Darrow et al., 2014). Ponatinib was approved based on a surrogate marker through the accelerated approval path in December 2012. “Emerging data showed that 24% of the patients who had been followed for a median of 1.3 years and 48% of those who had been followed for a median of 2.7 years had serious thromboembolic events, including myocardial infarction and stroke (Grady, 2013). The drug was allowed back on the market in December 2013 with more limited indications and a restricted distribution system.” (Darrow et al., 2014)

<sup>182</sup> Although how much of the increase in serious event reports is real is debatable, numerous reports in FAERS and other source seem to reflect reality. Sakaeda et al. state that “A debate recently published in a respected journal indicates both the advantages and limitations of data mining of spontaneously reported adverse event databases.....A report in the FAERS database is a story, sometimes only a rumor, but numerous reports can reflect reality. With larger numbers of faithful reports, the FAERS database and other spontaneously reported databases should help to optimize pharmacotherapy.” Sakaeda, T., Tamon, A., Kadoyama, K., & Okuno, Y. (2013). Data Mining of the Public Version of the FDA Adverse Event Reporting System. *International Journal of Medical Sciences*, 10(7), 796–803.

a sufficient method for detecting drug safety problems. As a result, the demand<sup>183</sup> for postmarketing requirements and commitments has risen.

In addition to the critiques and factors that contributed to more emphasis on postmarketing studies, issues with preapproval studies and study designs add to justification of the rationale for requirements and commitments after approval. “Preapproval studies are necessarily limited in size and tend to be narrow compared to postmarketing studies: preapproval trials generally seek subjects who are as homogenous as possible, in order to reduce unexplained variability in the outcome variables and increase the probability of detecting a difference between the study groups” (Strom et al., 2012). The increased sample size available after marketing also allows a more precise determination of the appropriate dose to be used (Cross et al., 2002; Heerdink, et al., 2002; Peck, 2003; Temple, 2003).<sup>184</sup>

Drug safety is not the only rationale for postmarketing studies. Studies discovered that the recent regulatory flexibilities for drug approval are related to approvals based on single, nonrandomized, or uncontrolled pivotal trials without patient relevant outcomes or adequate

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<sup>183</sup> Political demands can be seen in Congress and FDA’s responses. (1) Soon after rofecoxib’s withdrawal in 2004, hearings of the Senate Finance Committee and media raised serious questions about drug safety. In response, CDER asked the IOM to assess the U.S. drug-safety system which was published in 2006. (2) In 2005, the FDA formed the Drug Safety Oversight Board to advise the CDER, which was IOM’s recommendation. (3) PDUFA III (2002) and IV (2007) expanded budget appropriation for postmarketing regulation on drug safety. (4) Congress passed the FDAAA of 2007 that greatly emphasizes the role of postmarketing regulations for the drug safety such as requiring postmarketing studies, labeling revisions, and Risk Evaluation and Mitigation Strategies (REMS). (5) Congress passed Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 that expands FDA authorities to collect user fees to fund reviews of innovator drugs, introduces breakthrough therapy, and enhances the safety of the drug supply chain.

<sup>184</sup> Let us say that drug A resulted in an increase of 1 in 1000 deaths per year among patients. If the drug was only used among 1,000 people every year for a specific, relatively rare disease this might be a minor problem. But when the drug is widely used in a population where the average number of deaths per year was 1, 5, or 10 per 1,000 patients, the sample size necessary to identify an increase in 1%, 2%, or 3% of the deaths is very substantial and very difficult to find. (Kuller, interview)

participation of the minorities (Wallach et al., 2018; Kesselheim and Avorn, 2017; Downing et al., 2014<sup>185</sup>; Downing et al., 2016<sup>186</sup>).

Approving ineffective drugs can be costly and harmful. For example, ineffective antimicrobial drugs could cost lives and harm the public health by increasing drug resistance. Drugs for serious diseases like cancer might cost a lot when type I error (approving ineffective drug) occurs because high risk was compromised at the time of approval (benefit should be great in order to justify high risk). Furthermore, when pricey medicines do not perform as expected, the overall cost of health care may rise greatly.

Moreover, the primary outcome of more than 40% of pivotal trials used as the basis for approval of new indications is a surrogate that aims to substitute for and predict a final patient-relevant outcome (Ciani et al., 2017).<sup>187 188</sup> With the findings that many novel drugs are designated for expedited approval based on pivotal trials that are often small, short, and evaluate surrogate markers, it is not surprising that there is more demand for postmarketing studies.

Since the 1970s, more drugs have been approved with postmarketing requirements and/or commitments. Figure 3-1 below exhibits the percentage of new molecular entities (NMEs) with at least one postmarketing study over time since 1970. Despite some fluctuations, it clearly shows an upward trend: more NMEs are approved with at least one postmarketing study. Between 1970 and

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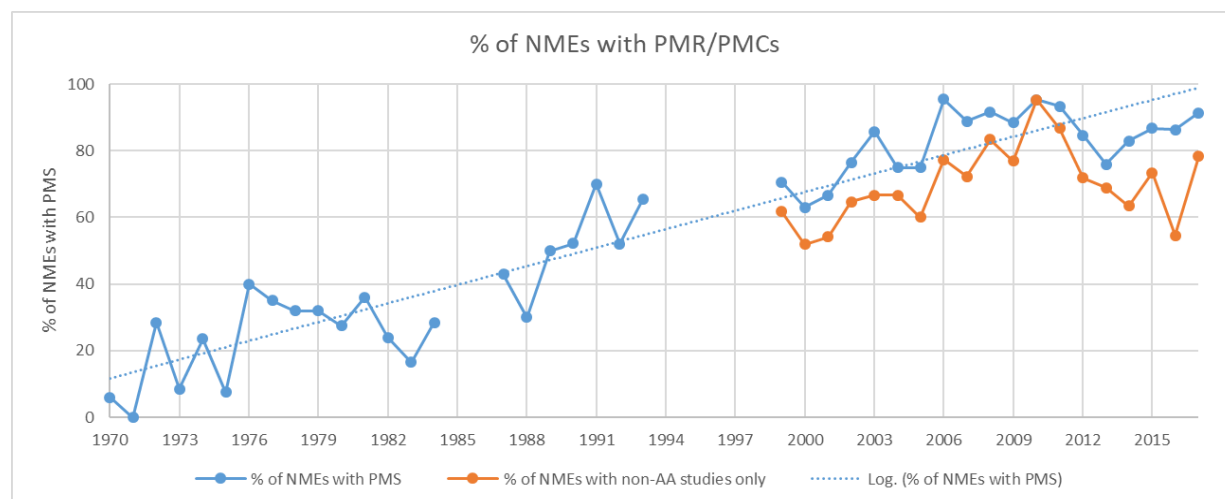
<sup>185</sup> Downing et al. (2014) found that, for the novel therapeutic agents approved between 2005 and 2012, 36.8% of indications were approved based on a single pivotal study. And, 44% of trials among non-accelerated approval therapeutics were based on surrogate endpoints

<sup>186</sup> Downing et al. (2016) found that elderly patients and from racial and ethnic minorities are underrepresented in the pivotal trials for novel drugs approved between 2011 and 2013.

<sup>187</sup> For oncology drugs, this proportion increases to two-third of all trials.

<sup>188</sup> The role of surrogate markers in health care remains “uncertain and concerning.” (Wallach et al., 2018; Fleming and Demets, 1996; Yudkin et al., 2011; Moynihan, 2011; Ciani et al., 2013; Ciani et al., 2016)

1975, the percentage of NCEs<sup>189</sup> with a postmarketing study averaged 12% (Mattison and Richard, 1987). Since 2008, on average, 87% of NMEs have been approved with at least one postmarketing study.



**Figure 3-1. Percentage of NMEs with at least one postmarketing study, 1970-2017**

**Notes:**

1. No dataset is available for NMEs with PMR/PMCs over a continuously extended period of time, and therefore this graph was derived from three different data sources: (i) Mattison and Richard data (NCEs approved during 1970-1984), (ii) Office of Inspector General (OIG) data (NMEs approved during 1987-1993), and (iii) author's own data (NMEs approved during 1999-2016)
2. The orange line shows the percentage of NMEs with non-AA studies only.

<sup>189</sup> An NCE is a drug that contains no active moiety that has been approved by FDA in any other application submitted under FDA Act § 505(b). FDA's classification of a drug as a NME for review purposes is distinct from FDA's determination of whether a drug product is an NCE within the meaning of the FD&C Act. Although their definitions are different, they are very similar in terms of characteristics of "newness."

### 3.2.3 Policy issues amid the increasing postmarketing studies

The growth in postmarketing studies and expedited drug approvals has stoked some policy controversies.<sup>190</sup> One relates to the unfulfilled or delayed postmarketing requirements and commitments. Some worry that the FDA's faster approval could increase the potential for previously unrecognized safety issues to appear when those drugs are widely used and postmarketing studies are not fulfilled (Darrow et al., 2014<sup>191</sup>; Moore and Furberg, 2014<sup>192</sup>; Carpenter et al., 2008; Carpenter et al., 2012<sup>193</sup>). United States Government Accountability Office (GAO) (2009, 2015) and OIG (1996, 2006, 2016) also recognized that FDA was not equipped with

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<sup>190</sup> On another account of policy issues related to postmarketing studies, one might argue that the FDA faces problems of protecting the public for almost absolute safety. No single regulatory system can guarantee absolute safety or effectiveness. This is an impossible task, but the public expects nearly absolute safety. For example, in their book *Perspectives on Risk and Regulation: The FDA at 100*, Daemmerich and Radin (2007) wrote "During the century since the passage of the 1906 Federal Food and Drug Act the public has come to expect nearly absolute safety when consuming the products of science-based firms." And, FDA's own credibility may be shrunk when approving bad drugs and when postmarketing regulation fails to ensure public health. The Agency's regulation power may depend on its credibility (in other words, reputation) and drug regulatory effect may be at stake if the agency reputation decreases (Carpenter, 2014; Carpenter and Krause, 2014).

<sup>191</sup> "Efforts to promote early access, expedited development, and early approval have existed for decades. Unfortunately, these efforts generally have not been followed by equally energetic efforts to develop rigorous confirmatory data that could refine the indications for the drug or even change its approval status... There has also been little discussion of the implications of approving breakthrough drugs on the basis of limited data for patients considering therapeutic options and for their physicians... Some have suggested that insurers will act as an effective counterweight in the postapproval marketplace by refusing to cover breakthrough products with clinical activity that is either unconfirmed or does not justify the high cost."

<sup>192</sup> "for new drugs approved by the FDA in 2008, those that received expedited review were approved more rapidly than those that received standard review. However, considerably fewer patients were studied prior to approval, and many safety questions remained unanswered." They found that, by 2013, many postmarketing studies had not been completed. "As many safety questions were not answered prior to drug approval, some patients may have been exposed to safety risks that had not been well characterized... The testing of new drugs has shifted from a situation in which most testing was conducted prior to initial approval to a situation in which many innovative drugs are more rapidly approved after a small trial in a narrower patient population, with extensive additional testing conducted after approval. Our findings suggest that the shift has made it more difficult to balance the benefits and risks of new drugs."

<sup>193</sup> Carpenter et al. (2008, 2012) argued that deadlines and time pressure (shortened review time) negatively affect the drug approval decisions of the FDA. Drugs approved just before the deadline are more likely to have postmarketing safety events once the drugs are in clinical use.

management tools for monitoring and enforcement associated with expedited approval process and PMR/PMCs.

Carpenter (2014) notes emerging concerns in applying the standards used for cancer and AIDS drugs to a wide range of drugs, especially when many firms and policymakers would like to see expedited approval of new drugs become the norm. This concern is growing because FDA's effort in accelerating drug development is expanding. Discussions in the last years include alternative pathways, enriched trials, an innovative program for biomedical innovation, and reduced efficacy standards for Alzheimer disease (FDA, 2014; Moore and Furberg, 2014).<sup>194</sup>

Kesselheim et al. reported in 2015 that expedited programs are becoming the norms rather than the exceptions. From 1987 to 2014, they reported a significant increase of 2.4% per year in the proportion of drugs with at least one expedited program (See Figure 3-3 in Appendix J). They concluded that there is “an increasing prevalence of expedited development and review programs that cannot be attributed to an increase in the number of innovative new drug classes over time. ... a majority of [new] drugs were associated with at least one of these special programs, meaning that the exceptions had become more common than the rule.”<sup>195</sup>

In sum, PMR/PMCs have been increasing for the past several decades and the demand for PMR/PMCs have risen all the more, resulting from fast approvals, lifecycle management, and safety concerns as well as the shortcomings of pre-approval and spontaneous reporting data. Researchers found an increasing number and percentage of expedited approvals and drug

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<sup>194</sup> Alternative pathways expedite the development of drugs by accepting studies in a smaller subpopulation of patients and labeling narrower indications in limited, well-defined subpopulations. Enriched trials allow patient selection before randomization based on the likelihood of response to the intervention.

<sup>195</sup> According to the FDA, 45% of new drugs were approved on the basis of a surrogate endpoint between 2010 and 2012 (FDA, 2015).

approvals based on surrogate markers. But, they also observed that many postmarketing studies for new drugs were delayed.

### **3.2.4 FDA Advisory Committee**

The FDA has a process for obtaining external expertise. “FDA reviewers complete an initial review of a product application and identify questions where external input is needed. The FDA then convenes an advisory committee meeting and obtains the requested input through a combination of presentations, discussion, and voting by committee members. After the meeting, FDA reviewers take into account the input received when making product approval decisions, although the recommendations of the committee are not binding.” (Smith et al., 2012)

The meeting agenda varies from approving new drug or new indication to developing guidance on a certain drug class. The FDA and sponsor prepare briefing materials and the Agency prepare the questions to ask the committees. “Briefing materials” are the package of information that the Agency provides to advisory committee members before a meeting. “If an advisory committee meeting is scheduled to address more than one topic, separate briefing materials may be prepared for the different topics on the meeting agenda” (FDA, 2008).<sup>196</sup> The materials are sent to the committee members in advance but they are not allowed to talk about any material outside the meeting room. (FDA, 2008)

These committees are composed of persons with some expertise regarding the drug application at hand, including scientific and medical experts, and representatives of relevant

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<sup>196</sup> <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125650.pdf>  
Guidance for Industry Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members, 2008



industry, consumer, or patient groups (Lavertu and Weimer, 2011). “Despite the Agency’s effort to standardize the committee process, each committee meeting remains a unique experience based on the product being reviewed, the makeup of the panel, and comments stated during the public comment period.” (Jackson et al., 2011)

Advisory committees communicate to the agency through discussions and voting. FDA learns from the discussion and exchange among advisory committee members during a meeting, and from individual recommendations and suggestions made. And, advisory committees often vote on a question or series of questions posed to the committee (voting and non-voting questions are provided by the Agency) during a meeting. (FDA, 2008)<sup>197</sup>

There are some advisory committee meetings without voting. For example, usually, there is no voting at meetings to discuss a clinical trial or study design or the development of a guidance document. At other times, members cast a formal vote on issues related to the approvability of a product submission or on different questions such as postmarketing studies. All members vote on the same question, many of the questions voted on are complex. FDA reviewers (participants) often mention that discussions are important not just voting results due to the complexity of issues they handle. For the integrity of voting, FDA adopts simultaneous voting instead of sequential voting to avoid potential risks (influencing sequential voters, etc.). (FDA, 2008)<sup>198</sup>

The FDA convenes advisory committees to discuss challenging cases. A drug application that is the subject of an advisory committee meeting can be considered a “difficult” case—difficult

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<sup>197</sup> <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125641.pdf>  
Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings, 2008

<sup>198</sup> <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125641.pdf>  
Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings, 2008

to judge whether the benefit outweighs the risk of a drug (but not necessarily because of uncertainty). The percentage of all NMEs subject to advisory committee meetings was 32.8% during 2001-2005 (Smith et al., 2012), 41.4% during 2006-2010 (Smith et al., 2012), and 38.1 % during 2012-2016 respectively. The 2007 FDAAA requires the FDA to hold advisory committee meetings for all NMEs or to provide rationale as to why not holding meetings. But only 38% of NMEs were referred to the committee meetings during 2012-2016. FDA usually provides some rationales for not convening advisory committees in administrative and correspondence documents.<sup>199</sup>

Advisory committees “provide independent, expert advice to the agency” on a wide range of issues.<sup>200</sup> Advisory committees mark the important step in evaluating drugs’ risk and uncertainty, and advisory committee decisions predict the agency’s drug approval decisions (Moffitt, 2010; Lavertu and Weimer, 2011; Smith et al., 2012). According to Smith et al. study (2012) that looked at the FDA committee meetings during 2001-2010, the FDA approved 88% of the original NDAs or BLAs that were endorsed by its advisory committees, and it did not approve 86% of those that the committees did not endorse. See Figure 3-6 in Appendix J.

Furthermore, using 1997-2006 drug and device approval data, Lavertu and Weimer (2011) showed that “an increase in the proportion of committee members voting for drug approval increases the probability of FDA approval and that an increase in the proportion of committee members voting for approval reduces the time it takes for the FDA to approve a drug or device

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<sup>199</sup> But the rationales provided are pretty much standardized: examples include: “Your application for xxx was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.” OR “Your application for xxx was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would have benefited from advisory committee discussion.”

<sup>200</sup> <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048040.htm>

application after committee consultation.” The FDA retains formal decision-making power, but, nevertheless, academic accounts suggest that committees wield influence over FDA decision making (Lavertu and Weimer, 2011). The FDA says that “as the agency makes its final decision, FDA seriously considers the recommendations made by advisory committees, including the advisory committee deliberations and voting.” (FDA, 2008)<sup>201</sup>

Although each advisory committee meeting is unique, many committee members demonstrate similar influences when considering the evidence at hand, according to a recent survey.<sup>202</sup> The survey (Burgess et al., 2015) found that while 60% spend equal time on sponsor- and FDA-prepared materials; panel members do indicate they are more heavily influenced by FDA-prepared materials. Additionally, a majority of committee members (70%) are influenced by the meeting itself: 81% indicated that the public hearing “sometimes to always” influences their vote (Burgess et al., 2015; Jackson et al., 2015).

### **3.3 Research questions, Methods, and Data**

#### **3.3.1 Research questions**

Several researchers have looked at accelerated approvals that, by statute, require postmarketing confirmatory trials. But, there has been little attention paid to the effect of the

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<sup>201</sup> <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125641.pdf> Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings, 2008

<sup>202</sup> RAPS. “What Influences CDER Advisory Committee Members?” May 15, 2015. Available at: <http://www.raps.org/regulatoryDetail.aspx?id=22193>

availability of postmarketing studies on the drug approval process itself and for the drugs without accelerated approvals.

The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) in 1962. The 1962 Amendments required drug companies to establish a drug's effectiveness by "substantial evidence" which was defined as "evidence consisting of adequate and well-controlled investigations" (FDA, 1998). Since the 1962 Amendments, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. According to the FDA (1998), with regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.<sup>203 204</sup>

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing (FDA, 1998). In some cases, FDA has relied on pertinent information from other studies to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In other cases, FDA has relied on only a single adequate and well controlled efficacy study to support approval<sup>205</sup> (FDA, 1998). In 1997, Congress amended section 505(d) of the Act<sup>206</sup> to make it clear that the Agency may consider "data from one adequate and well controlled clinical investigation and confirmatory evidence" to constitute

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<sup>203</sup> See Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); Warner-Lambert Co. V. Heckler, 787 F. 2d 147 (3d Cir. 1986)

<sup>204</sup> FDA's position is based on the language in the statute and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962)) (FDA guidance, 1998).

<sup>205</sup> Generally when a single multicenter study of excellent design provided highly reliable and statistically strong evidence, and a confirmatory study would have been difficult to conduct on ethical grounds

<sup>206</sup> FDA Modernization Act

substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.

In sum, the FDA had had a long-standing adherence on its “standard of proof” evaluating drugs’ risks and benefits since 1962 until the 1990s. But, since the 1990s, Congress allowed FDA’s discretion on judging the quality of evidence and the standard of proof. And, it is widely accepted that the FDA has administrative discretion to approve or reject drugs (and label changes).

With FDA’s flexibility on evaluating the quantity and quality of evidence, does the greater likelihood that PMR/PMCs will be conducted affect approval decisions in cases where evidence is relatively weak? If it does, how does it affect the approval process? By investigating these questions, I intend to shed light on the possible effect of postmarketing studies on the subsequent FDA’s drug approval process.

Here, I focus on FDAAA safety requirements and postmarketing commitments. Accelerated approval (AA) and Animal studies were designed to have postmarketing studies as conditions for approval. And, PREA studies wouldn’t affect the drug approval process because information that PREA can bring is unlikely to address the risk and benefit of the proposed indication for approval.

When the option of postmarketing studies is available, the trade-offs between approval with PMR/PMCs and rejecting approval may take place. Let us consider two scenarios. In the first scenario, the choice is between approval without postmarketing studies and rejection of the drug. In the second scenario, the choice is between approval without postmarketing studies, rejection of approval, and approval with postmarketing studies. It is plausible that the addition of the third option (approval with PMR/PMCs) will increase the odds of approval.

The underlying assumptions are that the costs of a mistaken approval will tend to be reduced because the existence of an error will be identified and thus corrected through postmarketing studies and that the advisory committees and FDA have desire to minimize the sum of error costs (error of not approving good drugs and error of approving bad drugs). And the error costs can be minimized by reducing uncertainty.

Uncertainty is one of the major factors of rejection of new drug applications by the FDA (Sacks et al., 2014).<sup>207</sup> Sacks et al. found that uncertainty with dosing was the most frequently cited factor (16%) concerning efficacy and adverse events as well as potential risks to untested study populations are most frequently cited factors concerning safety. The authors defined *uncertainty* as “inability to determine a suitable dose for drug labeling.”

If uncertainty is one of the major reasons that approvals are denied by the FDA, then how might postmarketing studies play a role in reducing uncertainty? Let us consider a case where benefits and risks of a drug may not be clearly well-defined at the pre-approval stage. Information available at the time of making approval decision may be inadequate in two respects: (1) data quality is “not good enough” to weigh a drug’s benefit over risk or (2) no information is available for a particular issue.<sup>208</sup>

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<sup>207</sup> Sacks et al. (2014, authors are FDA staff) looked at 151 NME applications, out of 302 total applications, that were rejected when first submitted to the FDA during 2000-2012. Some drugs inevitably failed due to lack of efficacy or safety and others failed due to inadequate data to evaluate safety or efficacy. The latter case is uncertainty.

<sup>208</sup> If a new drug application contains good information to judge the net benefit, the option of PMR/PMCs may not affect the approval decision. If a positive net benefit (benefit > risk) is well established, the drug would be approved. If a negative net benefit (benefit < risk) is clearly shown, the drug would not be approved. Some might say that postmarketing studies may be established even when pre-approval evidence is clear. But, it is less likely to be required in such cases. (Here, we are mainly concerned with FDAAA safety requirements. AA, Animal, and PREA studies are exceptions.) And, if required, it seems less likely that the approval decision would be influenced by the availability of postmarketing study options because the role of postmarketing studies is reducing uncertainty not replacing risk with benefit.

In both respects, lack of information makes it difficult to make the risk-benefit judgment. Uncertainty connotes unpredictability and uncontrollability. According to Toma et al. (2012), uncertainty refers to situations about which there is sufficient information to identify objective probabilities. Therefore, when the information necessary for understanding and anticipating developments, or changes that may occur in a particular context are either insufficient or unavailable, the situation is defined as uncertain. The first scenario of inadequate data in the previous paragraph is poor quality, “not good enough” data quality to weigh a drug’s benefit over risk and this is a situation where information is insufficient. The second scenario of inadequate data is unavailable information. Both cases fit the definition of “uncertainty.”

Postmarketing studies could help in making approval decisions by increasing the possibility of reducing uncertainty in the future. PMR/PMCs decrease the cost of approval by reducing uncertainties in the future, which ensures that the FDA and sponsors will have data about the shared concerns in the specified time.

This paper aims to answer whether postmarketing studies have any roles in approval process. How often do advisory committees discuss postmarketing studies? When they do, do they talk about them in relation to approval? When postmarketing studies address uncertainties, do we observe any evidence on the role of PMR/PMCs on approval process from dialogues from transcripts and interviews?

### **3.3.2 Methods**

In this paper, I employed qualitative content analysis on FDA advisory meeting transcripts and interviews. In order to address the effect of postmarketing study options on approval process, I looked at how FDA advisory committees discuss drug approval and postmarketing studies in the

committee meetings and what stakeholders who participate in committee meetings say about their approval process and PMR/PMCs. In addition, FDA's final decisions on approval and on requiring or requesting postmarketing studies were examined.

Since challenging cases brought to the FDA advisory committees are more likely to have uncertainties than ones without advisory committee meetings, it is more likely to find evidence of the effect of postmarketing studies on the drug approval process if any.

Another rationale for examining advisory committee meetings is that transcripts of their meetings provide one of the few windows on the FDA's drug approval process. Since the committee meeting transcripts contain conversations among the participants, we can observe and understand the dynamics and contexts of discourse on postmarketing studies and making recommendation for or against approval. Also, the transcripts provide, to some degree, outsider perspectives.

To capture any changes in the discussions of postmarketing studies and making approval decisions over the past couple of decades, I acquired advisory committee transcripts for 1985-1989 (Period 1) and 2012-2016 (Period 2). It is expected that more discussions on postmarketing studies would be observed in Period 2 since postmarketing studies are more readily available now compared to 30 years ago (the number of postmarketing studies and the percentage of drugs with studies have grown). And, because expedited approval paths were introduced since 1990s, especially, accelerated approvals, we expect to see larger effect of postmarketing study options on approval process in Period 2.

In addition, I interviewed FDA reviewers, medical professionals who have served in advisory committees, and staff from pharma companies. The objective of interviews was to add more nuance to and elaborate the findings from advisory committee meeting data analysis. The



interview question drafts can be found in Appendix L. Note that the questions were modified during interview based on the interviewee's expertise and experience with FDA as well as their answers.

Lastly, one might consider examining the effect of postmarketing studies on the drug approval process by using committee's voting results and FDA's approval decisions. I attempted such methods, but they didn't yield concrete results that could help answering the research question. The methods and findings using committee votes and FDA approval decisions can be found in Appendix R.

### **3.3.3 Data**

I used two different data sources: one is qualitative data from interviews and the other is advisory committee meeting transcripts. There are currently 13 drug/disease-specific advisory committees<sup>209</sup> and they meet 2-5 times per year on average. (See Figures 3-4 and 3-5 in Appendix J) In this study, I selected cardiovascular and renal, oncologic, anti-infective (anti-microbial), and gastrointestinal committees based on the number of meetings and comparable frequency of meetings between time period 1 (1985-1989) and time period 2 (2012-2016).

Table 3-7 in Appendix I describes the number of advisory committee meetings by year and by committee in time period 1 and time period 2. Some committees have more consistency in frequency of meetings over time periods than other committees. For example, anti-infective, cardiovascular and renal, gastrointestinal, and oncologic drug advisory committees have a sizable

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<sup>209</sup> There are non-disease/therapeutic-specific committees that discuss general issues and policies: Drug Safety and Risk Management Advisory Committee, Nonprescription Drug Committees, Pharmaceutical Science and Clinical Pharmacology Advisory Committee, and Pharmacy Compounding Advisory Committee

number of meetings in both Period 1 and Period 2. In this study, the sample includes these four committees.

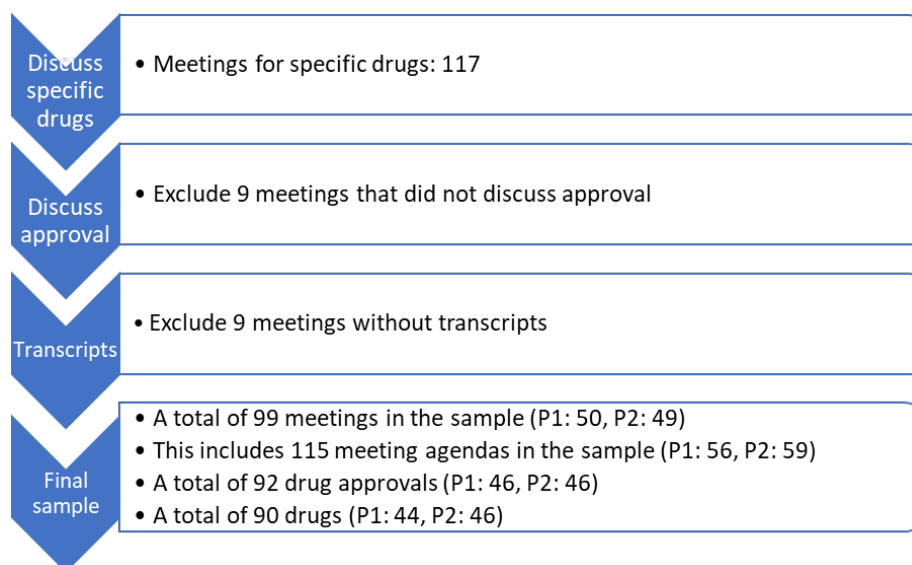
Figure 3-2 below shows the sampling process applied in this study. I sampled advisory meetings, in 4 advisory committees explained above, based on the following inclusion criteria: (1) meetings for a specific drug approval<sup>210</sup>; (2) availability of transcripts; and (3) time periods: 2012-2016 and 1985-1989<sup>211</sup>.

The units of analysis in this dataset are committee meeting, meeting agenda, drug approvals, and drugs depending on the question addressed. If there are more than one drug per meeting and if these are asked with separate individual questions, the meeting agendas are counted separately. For example, on 3/15/1998, the Gastrointestinal committee was convened to discuss Prilosec and they discussed three different indications with separate voting questions: (1) acute duodenal ulcer; (2) GERD; and (3) Z-E syndrome and hypersecretory states. Although it was one meeting (one day at the same venue), the committee discussed three agendas and all three had different voting results. Therefore, I separated the three meeting agendas.

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<sup>210</sup> There are advisory committee meetings where FDA and the committee do not discuss a specific drug approval. These meetings are convened to discuss hypothetical scenarios for drugs, to discuss FDA study guide, to discuss the use of patient reported outcomes (PROs) in the pediatric age group, to discuss possible pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, to discuss target population for a drug class, to discuss the benefits and risks of a drug class, to discuss clinical development programs and clinical trial designs, to provide advice on types of consumer studies, etc.

<sup>211</sup> The time period 1985-1989 was chosen because it provides a good amount of time difference between the time when postmarketing studies were less often available and today when PMR/PMCs became more readily available. Also, data availability was an issue—more often, only meeting minutes are available (not the transcripts) for earlier meetings.



**Figure 3-2. Advisory meeting sampling**

As shown in Table 3-2, a total of 115 advisory committee meeting agendas were included in the sample: 56 from 1985-1989 (Period 1) and 59 from 2012-2016 (Period 2). The Oncology committee discussed a total of 38 indications (33% of total sample) and Cardiovascular and Renal committee discussed 37 (32%) in Period 1 and Period 2. Antimicrobial committee and Gastrointestinal committee discussed 22 and 18 indications respectively, but sample sizes between Period 1 and Period 2 for these two committees are somewhat unbalanced (Antimicrobial committee discussed 4 in Period 1 and Gastrointestinal committee discussed 5 in Period 2.)

**Table 3-2. Committee meetings and drug approvals, by time-period and committee**

Committee	Period 1 (1985-1989)	Period 2 (2012-2016)	Total
Antimicrobial	4 (3)	18 (12)	22 (15)
Cardiovascular and Renal	21 (19)	17 (11)	38 (30)
Gastrointestinal	13 (11)	5 (4)	18 (15)
Oncology	18 (13)	19 (19)	37 (32)
Total	56 (46)	59 (46)	115 (92)

Note: the number in parenthesis is the number of drug approvals

After creating the list of advisory committee meetings, I coded meeting-relevant and drug-relevant variables. I used NDA/BLA numbers to link up drug approval data. I found NDA/BLA numbers in meeting minutes and transcripts whenever possible. When I couldn't find drug approval data (chemical type, expedited approval pathways, approval date, sponsors, brand or generic drug name), I used other web-based drug databases to locate such information. I also traced whether the drug was approved after the advisory committee meeting.

I classified the level of discussion as “discussed substantially”, “discussed”, and “not discussed.” To identify cases where postmarketing studies were discussed substantially, I counted the number of mentions on postmarketing studies and looked at the contents of discussions on those studies. Sometimes the sponsor and FDA present the existing postmarketing data (for new drug application but approved elsewhere or supplemental application) and the committee discuss them. I identified meetings where postmarketing studies were mentioned more than 10 times throughout the transcript as “discussed substantially.” If discussion is limited to the existing postmarketing data and not related to PMR/PMC options, I did not code the case as substantial discussion even if the word count exceeds 10.

And, I classified a discussion on postmarketing studies as “PMR/PMC discussion in the context of approval” if a postmarketing study was discussed in the following contexts: (1) pre-approval vs. post-approval study (timing decision on whether information is needed before approval or it can be acquired postmarketing); (2) having postmarketing studies is comforting (when concerns exist, the idea that PMR/PMCs address the concerns makes committee feel comfortable); (3) postmarketing studies as a condition for approval (committee mentions PMR/PMCs as a condition for approval); and (4) if approved, postmarketing studies should be done (committee wants postmarketing studies when approved). For more details on variables and

coding rules, see Table 3-6 in Appendix I. Discussion contents on postmarketing studies and approval are summarized in Table 3-4 in Section 3.4.2 and Appendix M.

Data availability issues arose in the drugs approved in the 1980s. After FDA drug approval database and google search, drug approval date information was not available for 4 drugs and whether a drug was approved is unknown for one of them. For the other three drugs, I was able to find the year of approval. I excluded the drug without approval information when an analysis requires drug approval data<sup>212</sup>. Furthermore, PMR/PMC data is rarely available for drugs approved in the 1980s. Approval letters for those drugs are largely unavailable on the FDA website and PMR/PMC dataset does not contain data in the 1980s.

Not all transcripts of committee meetings in the 1980s are available. I dropped 9 committee meetings in the 1980s because I had to rely on meeting minutes, not meeting transcripts.<sup>213</sup> Meeting minutes include discussion summary, the voting and discussion questions posed by the FDA, attending committee members, and voting results. But, detailed discussions on postmarketing studies are not presented in the meeting minutes and counting the number of PMR/PMC mentions is not possible.

Lastly, in addition to the advisory committee meeting data, qualitative data was acquired from interviews to supplement the advisory committee meeting data. A total of 12 interviewees<sup>214</sup> participated: 4 FDA reviewers, 5 FDA advisory committee members<sup>215</sup>, 2 from regulatory consulting firms (their clients are pharma companies), 1 from pharma companies, and 1 lawyer

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<sup>212</sup> I was not able to find out if the drug was approved (even after google search) and when the drug was approved.

<sup>213</sup> Out of 9 meetings, there was no discussion on additional or further studies based on meeting minutes (or any close indication for such discussions) in 5 meetings. I found two meetings where additional studies were mentioned according to the minutes but it is uncertain that it was specifically about postmarketing studies.

<sup>214</sup> I interviewed 13 people, but one (industry) of them had limited experience with FDA and postmarketing studies. And thus, I excluded the data from the interviewee from the analysis.

<sup>215</sup> One person served an FDA advisory committee and he works for a company.

whose clients are pharma companies. FDA advisory committee members were selected for interview based on the committees they serve<sup>216</sup>; I chose the committees that are not included in the content analysis sample<sup>217</sup>. Twenty-one CDER staff (directors and deputy directors of offices and divisions within CDER) were contacted for interview, one third of them responded and 4 FDA reviewers were interviewed.<sup>218</sup>

### **3.4 Findings**

In this section, I describe the findings from interviews as well as content analysis on advisory committee meeting transcripts in an attempt to answer the proposed research questions: How often do advisory committees discuss postmarketing studies? When they do, do they talk about them in relation to approval? When postmarketing studies address uncertainties, do we observe any evidence on the role of PMR/PMCs on approval process from dialogues from transcripts and interviews?

#### **3.4.1 PMR/PMC discussions in advisory committee meetings**

Table 3-3 below presents the overview of advisory committee meetings and discussions in the meetings for Period 1 and Period 2. It shows that, during 2012-2016, advisory committees discussed more postmarketing studies during the meetings. The percentage of advisory committee

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<sup>216</sup> Also, their accessibility and availability given time limitation.

<sup>217</sup> Four committee members are from other committees than the four committees in the sample for the transcript content analysis. One member served one of the four committees, but the interviewee is a pediatric specialist.

<sup>218</sup> Two CDER staff redirected me to FOIA request and Office of Regulatory Affairs, but that didn't yield interview opportunities.

meetings where a postmarketing study was discussed rose from 52% in Period 1 (1985-1989) to 85% in Period 2 (2012-2016). Because accelerated approval was introduced in Period 2 and accelerated approval is accompanied with confirmatory trials (PMRs), data without accelerated approvals are presented in the second column of Period 2 in Table 3-3. Even excluding accelerated approval in Period 2, the percentage of committee meetings where postmarketing study was discussed in Period 2 (82%) was much higher than in Period 1.

The average number of “postmarketing” mentions also increased, from 5.6 per meeting in Period 1 to 11.2 in Period 2. Furthermore, in Period 1, only four advisory committee meetings (7%) had extensive discussion of postmarketing studies and data compared to 20 (34%) in Period 2. Excluding accelerated approval, the average number of “postmarketing” study mentions (10.1) and the percentage of meetings where postmarketing studies were extensively discussed (26%) were much higher in Period 2 than in Period 1.

**Table 3-3. Advisory Committee (AC) meetings, postmarketing studies (PMS) discussed**

	<i>Period 1 (1985-1989)</i>	<i>Period 2 (2012-2016)</i>
The total number of ACs	56	59, 50
Number of ACs where PMS was discussed	29 (52%)	50 (85%), 41 (82%)
The average mentions on PMS per meeting	5.6	11.2, 10.1
PMS was extensively discussed	4 (7%)	20 (34%), 13 (26%)
PMS was discussed in the context of approval	12 (21%)	14 (24%), 8 (16%)

Notes:

1. Postmarketing study (PMS) is extensively discussed when (i) the committee discusses about the substance of postmarketing study not just postmarketing data and (ii) the number of mentions of postmarketing study  $\geq 10$ .
2. In period 2 column, the second number and percentage indicates the number of committee meetings excluding accelerated approval.

The frequency of discussions on postmarketing studies in relation to approval in Period 2 was higher (24%) compared to Period 1 (21%). But, when excluding accelerated approval discussions, the percentage of meetings where postmarketing studies were discussed in the context

of approval in Period 2 was 16% (8) which is lower than Period 1. This implies that the growth in discussion of postmarketing studies in the context of approval may be due to accelerated approval which was introduced in early 1990s. On the other hand, having discussion on postmarketing studies in the context of approval doesn't necessarily mean that there is a role of postmarketing studies on the approval process. See Section 3.4.2 for details.

And, the FDA more frequently posted a question on postmarketing studies to the committees during 1985-1989 (12) compared to the time period of 2012-2016 (8). A possible explanation is that the merit of having the option of postmarketing studies has decreased over time since many drugs are subject to postmarketing studies.

One caveat is that the number of meetings where postmarketing study was discussed with regard to approval (12 meetings) in Period 1 is highly concentrated in cardiovascular and renal committee. Ten out of 12 meetings were at the cardiovascular and renal committee. In Period 2, PMR/PMC discussion in the context of approval is evenly distributed across the committees. When adding accelerated approval discussions, committee meetings with PMR/PMC discussion in relation to approval increased significantly in oncology drugs, partly due to the introduction of accelerated approval (oncologic 6, cardiovascular 3, antimicrobial 2, gastrointestinal 3). See Table 3-8 in Appendix I.

Lastly, the difference in the percentage of advisory committee meetings with discussions on postmarketing studies across drug and approval types is smaller in Period 2 than in Period 1 (See Table 3-9 in Appendix I). For instance, during 1985-1989, 63% of new drugs and only 17% of supplemental approvals had discussions on postmarketing. The difference between new and supplemental has decreased in Period 2 (88% of new drugs and 63% of supplemental approvals had PMR/PMC discussion). The difference of percentage of AC meetings with PMR/PMC



discussion is more flattened among drug characteristics (new and supplemental approvals, NMEs and non-NMEs, NDAs and BLAs, review types, and orphan designation status) in Period 2. Also, the discussion shifted to more of postmarketing study design and implementation in Period 2.

### **3.4.2 Qualitative assessment on the role of PMR/PMCs on approval decisions from the meeting transcripts**

Excluding accelerated approval discussions, out of 115 meetings, a total of 20 had discussion on PMR/PMCs in the context of approval (89 had no discussion on postmarketing studies in the context of approval and 6 had discussion on accelerated approval).<sup>219</sup> Among them, in 4 meetings, I found some clues to indicate that committee members might use postmarketing studies as a tactic to make approval decisions more comfortably. But, such evidence on the role of PMR/PMCs on the drug approval process was not prevalent.

During period 1, there were 12 cases, and the evidence on the role of PMR/PMCs was unclear, too little, or absent. For example, in the discussion of a calcium channel blocker, Lidoflazine (1986 meeting, cardiovascular division), the sponsor suggested a role of postmarketing studies in addressing concerns: *“post-marketing surveillance is another opportunity to look at that issue.... In post-marketing surveillance, these risks can better be defined...”*

But the committee shared some concerns about post-approval regulatory actions when things fall out in the postmarketing data. FDA reviewer Lipicky asks *“what if, when the clinical*

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<sup>219</sup> Postmarketing studies can be discussed but not necessarily in the context of approval. For example, in the meeting for rociletinib (oncology) in 2016, the committee discussed trial design but not necessarily in the context of approval. For another example, in the meeting for filgrastim (oncology) in 2015, the committee discussed existing postmarketing data and postmarketing experience but not necessarily in the context of approval. In a meeting for vedolizumab (gastrointestinal) in 2013, the committee discussed the usefulness of postmarketing data, sponsor commitment to carry out postmarketing studies, postmarketing study types and designs, etc.

*trials went on in parallel, they found that, in fact, it did not work in that population? What would you do then? Let's say the scenario falls out that, in order to make this thing be available, one made it available and trials went on in parallel, postapproval, and the trials found it did not work in the population indicated. Then what would you do?"* An external consultant says *"The logic of that would be that it would be withdrawn."* And a committee member follows *"...the approval process should come after the data. We await the data with considerable interest. One other item we do not know about in these patients is the risk.....I think it is very hard to anticipate how these data will go."*

And, there was consensus on the lack of information about the drug (thus high uncertainty). A committee member said *"I think we would all await your studies and other studies showing that. It sounds like this is a very interesting drug, but I think without the data one can get misled."* And another member said *"...although it is uniquely effective ... it is uniquely risky. I think it is very hard to anticipate how these data will go."* All committee members voted no. In this case, although committee members discussed about PMR/PMCs, the possibility of a role of PMR/PMCs was not determinative in allowing the approval.

Another example is the discussion on Bepridil (1986 meeting, cardiovascular division). During the meeting, the general consensus was that more data would make the FDA and committee able to weigh the balance between benefit and risk of Bepridil (the issue was lack of data, thus high uncertainty). One committee member voted yes for approval with the idea that the likelihood of getting meaningful data premarketing is same as the likelihood of getting data postmarketing (voting result: 2 yes and 6 no): *"the likelihood that you are going to generate the kinds of data that are going to be full of clarity...they are not likely to appear in front of us.... approving it...is as likely to result in the generation of meaningful data..."* But, this doesn't provide evidence for the

role of PMR/PMCs on approval decision. Even if the member recommended approval with the idea that there will be postmarketing data, it doesn't mean that the member wouldn't recommend approval without postmarketing studies/data. This discourse is not the evidence for the role of postmarketing studies on approval decision.

In all other cases in period 1, there was no clear evidence on the role of postmarketing studies on the drug approval process despite some discussions about postmarketing studies in relation to approval. More detailed qualitative data can be found in Table 3-4 below and Appendix M.

**Table 3-4. Brief contents of discussion on postmarketing studies**

Year	Committee/Drug	Discussion contents on postmarketing studies and the level of role of postmarketing studies on approval process
1986	Cardiovascular/ Lidoflazine	PMS as an opportunity to learn safety issues, Pre- vs. Post-approval study <i>Little to no role of PMS on committee decision process</i>
1986	Cardiovascular/ Terazosin	PMS should be done, PMS design/purpose, Pre- vs. Post-approval study <i>Unclear role of PMS on committee decision process</i>
1986	Cardiovascular/ Esmolol	Pre- vs. Post-approval, efficacy data is needed <i>Unclear role PMS on committee decision process</i>
1986	Cardiovascular/ Elanpres	What should be done if approved? PM data should be collected <i>Role of PMS unclear</i>
1986	Cardiovascular/ nicardipine	Is confirmatory study necessary? What should be done if approved? Pre vs. Post-approval study <i>No role of PMS on committee decision process</i>
1986	Cardiovascular/ Bepridil	Need for more data to weigh benefit and risk, premarketing vs. postmarketing <i>Little to no role PMS on committee decision process</i>
1986	Gastrointestinal/ ethanolamine	Possibility of contingent approval with PMR/PMCs <i>No role of PMS on committee decision process</i>
1987	Cardiovascular/ Streptokinase	PMS would be beneficial, but it should not be a bar for approval, PMS should be done, PMS design <i>Role of PMS unclear</i>
1987	Cardiovascular/ ACTIVASE	PMS would be good, pre- vs. post-approval <i>Role of PMS unclear</i>
1987	Cardiovascular/ Milrinone	Sponsor suggests PMS if approved, more PM data would be helpful but the current data is not necessarily too uncomfortable <i>No role of PMS on committee decision process</i>
1988	Cardiovascular/	PMS plans, PMS as an approval condition, If not approving this drug, people will use more harmful drugs <i>No role of PMS on committee decision process</i>
1989	Anti-microbial/ Nebupent	Conditional approval and postmarketing study designs <i>No role of PMS on committee decision process</i>

Year	Committee/Drug	Discussion contents on postmarketing studies and the level of role of postmarketing studies on approval process
2012	Cardiovascular/ phenylephrine hydrochloride	Design of PMS, pre-approval vs. post-approval <i>Some role of PMS on committee decision-making process</i>
2013	Cardiovascular/ Tolvaptan	Postmarketing registry vs. trial, postmarketing risk management REMS <i>Little role of PMS on committee decision-making process</i>
2012	Gastrointestinal/ Humira	PMS influences approval decision, PMS should be done, proposed PMS <i>Some role of PMS on committee decision-making process</i>
2012	Gastrointestinal/ Gattex	Requirement vs. commitment, REMS vs. PMR/PMC, which is less burdensome? PM surveillance should be done, PMS design and recommendation <i>No role of PMS was observed</i>
2012	Anti-microbial/ raxibacumab	Animal rule, PMS option is on the table, PMS is important, purpose of PMS <i>Role of PMS is unclear</i>
2015	Oncologic/ Portrazza	Sponsor will do PMS, judgement should be based on what's available now <i>Some role of PMS on committee decision-making process</i>
2014	Oncologic/ Triferic	A member suggests a follow-up if approved <i>No role of PMS on approval</i>
2016	Anti-microbial/ solithromycin	Having PMS is comforting, PMS provides additional info in the real-world population, PMS design <i>Some role of PMS on committee decision-making process</i>

Notes: Excluding accelerated approval.

On the other hand, during period 2, I observed more evidence of alluding the role of PMR/PMCs on approval (see Table 3-4 above and Appendix M for further detailed quotes and discussions). Four out of 8 drugs had conversations that imply some role of PMR/PMCs on approval (these are not accelerated approvals). For example, a gastrointestinal committee member in August 2012 meeting where the committee discussed *Humira* (supplemental BLA for ulcerative colitis, non-expedited, orphan) talked about using postmarketing studies as a tool to deal with uncertainties:

*“Is there any role for this committee to think about what a postmarketing study might be if we felt that that could be influential in deciding whether to approve. And my understanding is yes, and that's part of what's going on in question number 5. My understanding is if you generally were concerned, but*

*thought that your best sense of the data was favorable benefit to risk, but you really had uncertainties about issues such as, is this the optimal dose, or we need to know more about safety, you could approve and then you could recommend that those studies be done as a way to alleviate some of the concerns you would have with approval if you were on the fence, so to speak.”*

Humira was originally approved for rheumatoid arthritis in 2002 and Abbott applied for a new indication for ulcerative colitis that was discussed in the 2012 meeting. Fifteen out of 17 voting members indicated a favorable benefit-risk profile (and FDA approved it with 6 FDAAA and 1 PMC <sup>220</sup>). And, this one committee member specifically talked about the role of

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<sup>220</sup> PMR #1: A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

PMR #2: A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-treatment with adalimumab and “switching” with other tumor necrosis factor (TNF)-blockers or biologics.

PMR #3: Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation final reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling.

PMR #4: Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

PMR #5: Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.

postmarketing studies on making approval decision under uncertainty. This remark provides a very clear evidence on the effect of postmarketing studies to make recommendation for approval easier.

Also, in discussing *phenylephrine hydrochloride* (NDA, non-NME, and non-expedited) in 2012, a cardiovascular committee member expressed the agony of not approving the drug and explained what could have won the approval:

*“I voted no .....I am sympathetic, however, to the situation of patients undergoing general anesthesia who may have a specific need for the agent, and I would think that maybe a very narrowly worded indication with a post-marketing, either some type of either study or some other type of post-marketing data collection looking at safety in that population would make sense.”*

In this meeting, the committee expressed concerns on approval for a broad indication and safety issues (voting result was 2 yes and 8 no, but FDA approved it with 1 PREA). This remark is not as clear evidence as the previous one, but this committee member clearly recognized the role of postmarketing studies on drug approval decision-making.

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PMR #6: A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

PMC #7: Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect samples for immunogenicity testing (utilizing a validated AAA assay as described in PMR #3 above) and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

Another member of Antimicrobial committee explained his alternative vote in the 2016 meeting for *solithromycin* (NDA, NME, priority review). In this meeting, the majority of the committee indicated that the risk of hepatotoxicity had not been adequately characterized, primarily due to the small size of the safety database. The vote was split: 7 yes and 6 no (FDA rejected). In discussing postmarketing studies and approval, a member argued that more detailed postmarketing plans could have changed his vote from no to yes. This isn't a strong evidence for the role of PMR/PMCs on the drug approval process, but he acknowledges that better quality of postmarketing plan could sway a vote:

*“I actually asked a question which could have swayed my vote. I was trying to give the sponsor a potential out because they were putting this great surveillance in place. And so I asked them, what level of signal will make you pause, make you stop, make you hold, make you withdraw, and I couldn't get an answer. If they would have told me one or two cases would make them pause, I could have voted yes with an understanding that they would try to work out some sort of an understanding with the FDA”*

The final case is a meeting on *Portrazza* (oncologic BLA, non-NME, fast track, orphan) in 2015. During the meeting, an FDA reviewer mentioned that a safety study will be considered if they were going to move toward an approval. But, some committee members shared a concern on the currently available data that makes judgment on benefit-risk ratio difficult. Then, a temporary voting member (consumer representative) said that she would feel comfortable if good monitoring is assured. Although there was no voting (FDA approved it without PMR/PMCs), her remark

shows that she was willing to take a chance if good monitoring was assured after marketed and her comments hint some possible role of postmarketing studies on drug approval:

*“...if I could be assured that people are going to have those good monitoring and good discussions about the risks/benefits for patients, I can feel comfortable with this moving forward.”*

In sum, compared to the time period of 1985-1989, more direct and explicit discussions of postmarketing studies are observed in decision making process today. Although the frequency of discussion of PMR/PMCs in the context of approval was higher in period 1, such discussion was mostly limited to the timing decision on requiring further data (i.e. requiring data pre-approval vs. post-approval) and postmarketing as a condition for approval. These discussions did not rise to the possibility of postmarketing studies as a tool to alter decisions or to help make decisions more easily. Again, discussing the option of PMR/PMCs as a condition for approval (for example, “I want this drug to be approved, but PMR/PMCs should be done”) doesn’t mean that the approval shouldn’t be granted without the PMR/PMCs. Although the existing evidence in period 2 was not abound (only 4 out of 59), such evidence on the role of PMR/PMCs surely exists.

Three out of four cases that showed some evidence on the role of PMR/PMCs on the drug approval process are either expedited approval drug or orphan drug. Also, in all four cases where committee members mentioned about the role of postmarketing studies in their decision making, the issue was uncertainty due to lack of data and inadequately characterized safety issues. It may be because postmarketing studies tend to address safety issues rather than efficacy issues. Other than confirmatory PMRs for accelerated approval and PREA studies, there aren’t many



postmarketing studies on efficacy (most of efficacy PMCs are continuing studies or submitting the final report of existing studies). One caveat is that there was no evidence that one member's opinion swayed other members' votes or opinions in reviewing the transcripts.

### **3.4.3 Findings from interviews**

#### **3.4.3.1 Effect of PMR/PMCs on the approval process**

Interview data indicates that 6 out of 12 interviewees recognized some role of PMR/PMCs on the approval process under certain circumstances (see Appendix K). Among the six who recognized the role, two were advisory committee members, three were FDA staff, and one was from industry. Three out of 12 interviewees indicated that the option of PMR/PMCs doesn't really affect approval decision or the role is very limited (1 FDA reviewer, 2 advisory committee members). Finally, data from 3 interviewees (2 industry, 1 committee) didn't provide strong evidence for their judgment on the effect of postmarketing studies on approval.

Regarding the effect of PMR/PMCs on making recommendation for approval, committee members had divided views. A committee member (interviewee #3) said having the option of postmarketing studies has no influence on approval process, but added that "sometimes, so, they justify their yes votes (recommending approval) with postmarketing studies." It is possible to mean that they would not vote yes. Interviewee #2 (committee) said "if there was going to be no additional data collection, the committee would have been more reluctant to recommend it."<sup>221</sup>

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<sup>221</sup> Endocrinologic and metabolic drugs advisory committee

### **3.4.3.2 Signaling postmarketing studies will be carried out**

When the FDA makes statements such as “FDA will be receptive of postmarketing studies,<sup>222</sup>” it telegraphs to the committee that there will be postmarketing studies (interviewee #2, committee). However, some committee members (interviewee #3, 12, 13) believe that firms bring up postmarketing studies because they want the committee to feel more comfortable recommending the drug, but the sponsors’ motivation to do well is low after approval. When companies say they will carry out PMR/PMCs, it is not convincing unless they provide detailed plans, interviewee #12 (committee) says.

### **3.4.3.3 Role of the existence of alternative therapy on approval process**

PMR/PMC may not be a greater factor than the availability of existing therapies. If there are no alternatives, the drug is more likely to be recommended for approval with less regard to postmarketing studies. For instance, interviewee #4 (committee) said s/he would not have recommended a drug regardless of postmarketing study option if there had been an alternative drug. The interviewee says “If they (FDA) said there will be no postmarketing studies, I would still recommend approval because of drug availability. Postmarketing study is not a greater factor than demand for a drug.” And, interviewee #12 (committee) said that alternative drug availability (e.g. drugs for rare diseases) affects decision-making on recommendation for approval.

Another reviewer dealing with drugs for small population (interviewee #8, FDA) argues that PMR/PMCs influence decisions for drugs for rare diseases. For the last ten years, most rare

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<sup>222</sup> “These studies are going to be required post-marketing studies. So to that extent, that's where we have the regulatory teeth to ensure that they get us that information. I mean if they don't get that information because of complacency or whatever on a company's part, then there are penalties that can be applied.” June 28, 2016 EMDAC meeting, discussing cardiovascular risk assessment plan for type 2 diabetes drugs

disease drugs got PMR/PMCs (interviewee #8). Interviewee #10 (FDA) pointed out, PMR/PMC options affect approval, but it is hard to quantify it.

The four FDA reviewers (interviewee #6, 7, 8, 10) agreed that today's problem in drug regulation lies in drugs treating small number of patients because drugs are getting specialized and being tested on fewer patients—e.g. oncologic drugs. The reviewers also identified the existence of alternative treatments as an important factor in the approval process (interviewee #6, 8, 10). Their view is consistent with the views from committee members.

#### **3.4.3.4 Increase in the number of PMR/PMCs**

FDA reviewers (interviewee #6, 7, 8, 10) attributed the increase in postmarketing studies to the 2007 FDAAA and more attention to drug safety, and to the increase in expedited approvals, but every division is different in terms of establishing PMR/PMCs. For instance, the cardiovascular division doesn't establish as many postmarketing trials as the oncology division because cardiovascular drugs are usually studied in trials with several thousand patients<sup>223</sup> (unlike more specialized cancer drugs), and they have good information on drug safety profile (interviewee #6, 7, FDA). And, note that cardiovascular drugs are less likely to be accelerated approval. In addition, interviewee #7 (FDA) mentioned that the division doesn't approve drugs that don't meet the evidentiary standard<sup>224</sup>, implying that the availability of PMR/PMC options does not affect approval decision.

However, interviewee #6 (FDA) says that more postmarketing studies are expected in the future because we will have less data preapproval on the narrower populations that will be targeted.

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<sup>223</sup> For anti-coagulant, up to 20,000 patients

<sup>224</sup> FDA's standard on substantial evidence requirement is two statistically significant clinical trials for efficacy and the benefit outweighing the risk.

For example, HIV trials are getting smaller and we have less data. The interviewee argues that, for oncology and anti-viral drugs, PMR/PMCs play important roles. It is because “huge demand” is on early approval and “people are willing to approve drugs with less data.”<sup>225</sup>

### 3.4.3.5 Enforcement

On the issue of enforcement concerning PMR/PMCs, FDA reviewers have a different view from advisory committee members and industry. They say that the FDA tracks and follows up with PMR/PMCs, and postmarketing studies are managed well (interviewee #6, 7, 10, FDA). Requirements are mandated by law, and thus firms have to carry them out, the reviewers say. They also noted that companies seem motivated—FDA views companies as reasonably responsive.<sup>226</sup>

On the other hand, the industry views PMR/PMCs as somewhat important at the time of approval, but many firms quickly lose interest in taking up their PMR/PMCs after approval. Interviewees #9 and #11 from industry believe that the PMR/PMCs play some roles in FDA’s decisions. Their comments were not limited to accelerated approvals—rather, they were addressing the role of postmarketing studies in general. Also, they think “more speedy approval” today is one of the causes for increasing PMR/PMCs. Interviewee #9 (industry) said, “Trade-offs between approving drugs faster with postmarketing studies and delaying approval happen. It is unreasonable to think it doesn’t happen. FDA is under pressure to approve drugs fast and given

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<sup>225</sup> The interviewee said “I think people are willing to approve drugs with less data—but it may not be much about safety data but more of routine studies like pharmacological studies that can wait until approval. So whatever and however data available in the first application can be used to determine approval if they feel it is enough and the rest can be examined after approval. But I recommend that you talk to other divisions.” The interviewee’s comment was not limited to accelerated approval.

<sup>226</sup> In 1989 Anti-infective AC meeting, Commissioner Young said “I have spoken to the president of the Company and CEO on more than one occasion and I am confident that he will do those studies from what he has assured me. Secondly, if they ever wish to come back to the Food and Drug Administration again -- “

the pressure, FDA mandates PMRs so that it can make right decisions—fix it later if something wrong found or make sure their approval was well founded.”

Furthermore, interviewees #1 (industry), #9 (industry), and #12 (committee) say, “companies say they will carry out postmarketing studies, but they (just) say it,” “no one cares about PMR/PMCs after approval and FDA says it follows up PMR/PMCs, but it doesn’t” and “it is toothless when it does.” Incentive for approval is big and penalty for not complying is low. Interviewees #1 and #9 say that firms will agree to everything FDA asks before approval but will be slow in carrying out PMR/PMCs after approval. The reasons can be: (1) some PMR/PMCs can be big burden for small firms; (2) recruiting patients can take longer; and (3) bad results are risky for their business.

#### **Summary findings from interview**

- FDA advisory committee members argue that PMR/PMCs can be a factor in making decision on recommending approval, but certainly not the most significant factor.
- Industry views PMR/PMCs as somewhat important at the time of approval and the trade-offs take place, but PMR/PMCs may not be the priority after the drugs get approved.
- FDA reviewers imply that “approving drugs with less data” might happen in some circumstances—rare diseases, narrow target population, and huge demand on fast approval. (When the FDA reviewers mentioned about this, the discussion was not limited to accelerated approval.)
- Identified factors that influence approval decisions include the unmet need and the availability of alternatives.

### 3.5 Discussion and Conclusions

Advisory committees discuss about postmarketing studies more often and explicitly when considering approvability today compared to 30 years ago. This trend is observed across FDA divisions under CDER and drug characteristics. Also, there is more explicit evidence for the role of postmarketing studies on approval today. In the 1980s, there were discussions on requiring studies and additional data as well as deciding whether studies should be performed pre-approval versus post-approval. On the other hand, in the 2010s, some evidence, albeit uncommon, on the role of postmarketing studies on approval was found.

Remarks from the gastrointestinal committee member (mentioned in Section in 3.4.2), *"those [postmarketing] studies be done as a way to alleviate some of the concerns you would have with approval if you were on the fence, so to speak"*<sup>227</sup> in the 2012 *Humira* meeting, were very explicit. This explicit discussion is very rare, but it surely happens and implies that the option of postmarketing studies has potential effect on making approval (recommending approval) decisions.

On the other hand, the FDA and industry professionals might be aware of the possibility of the effect of the postmarketing study options on approval decision-making. When problems or issues come up, it is not unusual for sponsors to mention the possibility of postmarketing studies and their plan to carry out those studies. Sometimes the FDA staff do so. For instance, in an Antimicrobial committee meeting in 2012, an FDA staff responded to a question posed by a committee member as follows:

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<sup>227</sup> In all four meetings with some evidence for the role of postmarketing study on the approval process, given limited time to speak per person, their discussions didn't last long.

*“...So one of the things that we benefit from the Advisory Committee is if the Committee should recommend approval, and if the Agency should approve this product, we certainly have options to be discussing, for example, post-marketing commitments with the sponsor, and that's certainly something that could be on the table, so we really appreciate your thoughts on that.”<sup>228</sup>*

The influence of PMR/PMC option on drug approval is also supported by interviews. Most advisory committee members, FDA reviewers, and industry professionals agreed that postmarketing studies have some influence on the approval process under certain circumstances. They identified specialized drugs (with small population), drugs for rare diseases, and drugs with great demands (no alternative) as most-likely influenced group. During 2012-2016, 58% of Oncologic committee members voted for approval for 14 drugs with PMR/PMC discussions but only 8% voted for approval for 5 drugs without PMR/PMC discussion. And, orphan drugs are more likely to be approved (or favored) when committees discussed postmarketing studies.

Also, three out of four cases with remarks on the role of PMR/PMCs on the approval process were expedited or orphan drugs with high medical needs. Synthesizing the findings from interview and meeting transcripts, it may be the case that people would be more willing to think about the option of postmarketing as a way of hedging against uncertainties and thus supporting approval, when medical demands and safety issues exist.

Lastly, this study doesn't aim to claim a normative argument—whether the effect of the option of postmarketing studies on approval decision is good or bad. One might question why we

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<sup>228</sup> Postmarketing studies were discussed, including the issue this FDA staff referred to.

need expensive postmarketing studies if they don't have any effect on easing uncertainty at the time of approval. The other might argue that postmarketing studies should not affect drug approval decision and their purpose should be limited to regulate drugs in the postmarket settings. This question requires further examination on the cost and benefit of the tradeoffs. Nevertheless, this paper is the first attempt to address this question by looking at the advisory committee meeting transcripts that are valuable source of data. Future researchers can take a further step from here.

### **Limitations**

One of the threats to validity is selection bias. I chose four advisory committees based on the number of meetings and the consistency of the frequency of meetings between the two time-periods. To decrease the threat, I aimed to interview advisory members in the committees other than the four advisory committees selected in the content analysis. Three of five advisory committee members I interviewed belonged to other committees than the four selected.

Also, this study has the limitations of studies on drug approval decision-making. In particular, we cannot control for the level of pre-approval benefit and risk as well as net benefit. It is challenging to capture all factors affecting approval decisions (weighing the efficacy and safety). The existing literature on drug approval do not quantify the level of evidence of safety and efficacy profiles of drugs reviewed. Even the FDA does not explicitly quantify the level of efficacy and safety (perhaps for political reasons as well). Lack of control for the level of pre-approval evidence on efficacy and risk of drugs makes it difficult to examine the causal inference in this study.

Data from interviews and transcripts rely on individuals' thinking and decision-making process. And much of evidence are suggestive rather than confirmatory due to the nature of "indirect" evidence. Also, the evidence of the role of postmarketing studies on approval came from



one or two individuals in a committee. A committee member's comments wouldn't necessarily represent the consensus of the committee members.

Finally, transit from the committee decision to FDA's final decision on approval remains largely unknown. Although FDA's approval decision is aligned with committee recommendations for the most part, we do not observe FDA's internal decision making.

### Bibliography for Study 3

- Avorn, J. (2004). *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs*, 108. New York, N.Y. Knopf.
- Bakke, O. M., Manocchia, M., Abajo, F., Kaitin, K. I., & Lasagna, L. (1995). Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: a regulatory perspective. *Clinical Pharmacology & Therapeutics*, 58(1), 108-117.
- Burgess, L., Cox, V., Regeer, B. (2015). What Influences CDER Advisory Committee Members? *Regulatory Focus. RAPS*.
- Carpenter, D. P. (2004). The political economy of FDA drug review: processing, politics, and lessons for policy. *Health Affairs*, 23(1), 52-63.
- Carpenter, D., Zucker, E. J., & Avorn, J. (2008). Drug-review deadlines and safety problems. *New England Journal of Medicine*, 358(13), 1354-1361.
- Carpenter, D., Chattopadhyay, J., Moffitt, S., & Nall, C. (2012). The complications of controlling agency time discretion: FDA review deadlines and postmarket drug safety. *American Journal of Political Science*, 56(1), 98-114.
- Carpenter, D. (2014). Can expedited FDA drug approval without expedited follow-up be trusted?. *JAMA internal medicine*, 174(1), 95-97.
- Chary, K. V. (2016). Expedited drug review process: Fast, but flawed. *Journal of Pharmacology & Pharmacotherapeutics*, 7(2), 57–61. <http://doi.org/10.4103/0976-500X.184768>
- Ciani, O., Buyse, M., Garside, R., Pavey, T., Stein, K., Sterne, J. A., & Taylor, R. S. (2013). Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. *Bmj*, 346, f457.
- Ciani, O., Buyse, M., Drummond, M., Rasi, G., Saad, E. D., & Taylor, R. S. (2016). Use of surrogate end points in healthcare policy: a proposal for adoption of a validation framework. *Nature Reviews Drug Discovery*, 15(7), 516.
- Ciani, O., Buyse, M., Drummond, M., Rasi, G., Saad, E. D., & Taylor, R. S. (2017). Time to review the role of surrogate end points in health policy: state of the art and the way forward. *Value in Health*, 20(3), 487-495.
- CSDD, Kaitin KI, editor. FDA requested postmarketing studies in 73% of recent new drug approvals. Tufts Center for the Study of Drug Development Impact Report. 2004 July/August;6(4)

- CSDD, Kaitin KI, editor. Challenges loom for postmarketing study commitments; benefits unclear. Tufts Center for the Study of Drug Development Impact Report. 2007 May/June;9(3)
- CSDD, Kaitin KI, editor. Postmarketing studies are becoming the norm in U.S., Europe, and Japan. Tufts Center for the Study of Drug Development Impact Report. 2008 July/August;10(4)
- Darrow, J. J., Avorn, J., & Kesselheim, A. S. (2014). New FDA breakthrough-drug category—implications for patients. *New England Journal of Medicine*, 370(13), 1252-1258.
- Downing, N. S., Aminawung, J. A., Shah, N. D., Krumholz, H. M., & Ross, J. S. (2014). Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *Jama*, 311(4), 368-377.
- Downing, N. S., Shah, N. D., Neiman, J. H., Aminawung, J. A., Krumholz, H. M., & Ross, J. S. (2016). Participation of the elderly, women, and minorities in pivotal trials supporting 2011–2013 US Food and Drug Administration approvals. *Trials*, 17(1), 199.
- Downing, N. S., Shah, N. D., Aminawung, J. A., Pease, A. M., Zeitoun, J. D., Krumholz, H. M., & Ross, J. S. (2017). Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *Jama*, 317(18), 1854-1863.
- Fain, K., Daubresse, M., & Alexander, G. C. (2013). The food and drug administration amendments act and postmarketing commitments. *Jama*, 310(2), 202-204.
- US Food and Drug Administration (1998). Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072008.pdf>
- US Food and Drug Administration (2004). Innovation or stagnation. Challenge and Opportunity on the Critical Path to New Medical Products. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf>
- US Food and Drug Administration (2011). Guidance for industry: postmarketing studies and clinical trials—implementation of §505(o)(3) of the Federal Food, Drug, and Cosmetic Act (April 2011). Retrieved from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.
- US Food and Drug Administration (2007). Guidance: Drug Safety Information – FDA’s Communication to the Public. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072281.pdf>

- US Food and Drug Administration (2009). Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>
- US Food and Drug Administration (2012). Guidance: Drug Safety Information – FDA’s Communication to the Public. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf>
- US Food and Drug Administration (2013). Guidance for Industry: Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act. CDER and CBER, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>
- US Food and Drug Administration (2013). Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need; Public Hearing. <http://www.fda.gov/Drugs/NewsEvents/ucm335680.htm>
- US Food and Drug Administration (2015). White Paper: FDA and Accelerating the Development of the New Pharmaceutical Therapies. <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM439183.pdf>
- Fleming, T. R., & DeMets, D. L. (1996). Surrogate end points in clinical trials: are we being misled?. *Annals of internal medicine*, 125(7), 605-613.
- Frank, C., Himmelstein, D. U., Woolhandler, S., Bor, D. H., Wolfe, S. M., Heymann, O., ... & Lasser, K. E. (2014). Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals. *Health affairs*, 33(8), 1453-1459.
- U.S. Government Accountability Office (2009). NEW DRUG APPROVAL: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints. September 2009. GAO-09-866. Retrieved from <http://www.gao.gov/assets/300/295762.pdf>
- U.S. Government Accountability Office (2015). FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement. December 2015. GAO-16-192. Retrieved from <http://www.gao.gov/products/GAO-16-192>.
- Gottlieb, S. (2016) FDA Needs to Change How it Regulates Novel Technologies. *Forbes*. Jan 12, 2016 <https://www.forbes.com/sites/scottgottlieb/2016/01/12/fda-needs-to-change-how-it-regulates-novel-technologies/#2636756c191e>
- Grabowski, H. G., & Vernon, J. M. (1983). *The Regulation of Pharmaceuticals: Balancing the Benefits and the Risks*. Washington, D.C.: American Enterprise Institute.

- Grabowski, H. G., & Wang, Y. R. (2006). The quantity and quality of worldwide new drug introductions, 1982–2003. *Health Affairs*, 25(2), 452-460.
- Grabowski, H., & Wang, Y. R. (2008). Do faster Food and Drug Administration drug reviews adversely affect patient safety? An analysis of the 1992 Prescription Drug User Fee Act. *Journal of Law and Economics*, 51(2), 377-406.
- Grady, D. (2013). Serious danger of blood clots halts sales of leukemia drug. *New York Times B*, 4.
- Hutt, P. B. & Merrill, R. A. (1980). *Food and drug law: cases and materials*. Foundation Press.
- Institute of Medicine (2007). *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice, Institute of Medicine.
- Institute of Medicine (2012). *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs,
- Board on Population Health and Public Health Practice, Institute of Medicine. Retrieved from [http://www.ncbi.nlm.nih.gov/books/NBK200905/pdf/Bookshelf\\_NBK200905.pdf](http://www.ncbi.nlm.nih.gov/books/NBK200905/pdf/Bookshelf_NBK200905.pdf)
- Johnson, J. R., Ning, Y. M., Farrell, A., Justice, R., Keegan, P., & Pazdur, R. (2011). Accelerated approval of oncology products: the food and drug administration experience. *Journal of the National Cancer Institute*, 103(8), 636-644.
- Jackson, J., Braccio, N., Brevig, H., Sengupta, D. (2011) *FDA Advisory Committee Trends Since FDASIA*, Avalere
- Kaitin, K. I., Mattison, N., Northington, F. K., & Lasagna, L. (1989). The drug lag: an update of new drug introductions in the United States and in the United Kingdom, 1977 through 1987. *Clinical Pharmacology & Therapeutics*, 46(2), 121-138.
- Kesselheim, A. S., & Avorn, J. (2017). New “21st Century Cures” legislation: speed and ease vs science. *Jama*, 317(6), 581-582.
- Kesselheim, A. S., Wang, B., Franklin, J. M., & Darrow, J. J. (2015). Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ* 2015;351:h4633.
- Kesselheim, A. S., & Darrow, J. J. (2015). FDA designations for therapeutics and their impact on drug development and regulatory review outcomes. *Clinical Pharmacology & Therapeutics*, 97(1), 29-36.
- Lavertu, S., & Weimer, D. L. (2011). Federal advisory committees, policy expertise, and the approval of drugs and medical devices at the FDA. *Journal of Public Administration Research and Theory*, 21(2), 211-237.

- Marwick, C. (1997). Concern expressed about FDA reform legislation. *JAMA*, 278(6), 459-459.
- Mattison, N., & Richard, B. W. (1987). Postapproval Research Requested by the FDA at the Time of NCE Approval, 1970–1984. *Drug Information Journal*, 21(3), 309-329.
- Mendeloff, J. M. (1995). Decision Analysis and FDA Drug Review: A Proposal for Shadow Advisory Committees. *Risk*, 6, 203.
- Moffitt, S. L. (2010). Promoting agency reputation through public advice: Advisory committee use in the FDA. *The Journal of Politics*, 72(03), 880-893.
- Moore, T. J., & Furberg, C. D. (2014). Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US Food and Drug Administration: the class of 2008. *JAMA internal medicine*, 174(1), 90-95.
- Moynihan, R. (2011). Surrogates under scrutiny: fallible correlations, fatal consequences. *BMJ: British Medical Journal (Online)*, 343.
- Muñoz, M. (2016). Introduction to Post-marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER. FDA. <https://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM487405.pdf>
- Naci, H., Smalley, K. R., & Kesselheim, A. S. (2017). Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *Jama*, 318(7), 626-636.
- Naci, H., Wouters, O. J., Gupta, R., & Ioannidis, J. (2017). Timing and characteristics of cumulative evidence available on novel therapeutic agents receiving Food and Drug Administration accelerated approval. *The Milbank Quarterly*, 95(2), 261-290.
- Olson, M. K. (1995). Regulatory agency discretion among competing industries: inside the FDA. *Journal of Law, Economics, & Organization*, 379-405.
- Olson, M. K. (2008). The risk we bear: the effects of review speed and industry user fees on new drug safety. *Journal of health economics*, 27(2), 175-200.
- Parver, D. G. (1999). Expediting the drug approval process: An analysis of the FDA Modernization Act of 1997. *Admin. L. Rev.*, 51, 1249.
- Pease, A. M., Krumholz, H. M., Downing, N. S., Aminawung, J. A., Shah, N. D., & Ross, J. S. (2017). Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *bmj*, 357, j1680.
- Peltzman, S. (1972). The benefits and costs of new drug regulation. University of California.
- Peltzman, S. (1974). Regulation of pharmaceutical innovation: The 1962 amendments. American Enterprise Institute for Public Policy Research, 15.

- Quirk, P. J. (1981). *Industry influence in federal regulatory agencies*. Princeton University Press.
- Quirk, P. J. (1980). Food and Drug Administration. in *The politics of regulation* (Wilson, J. Q., 1980).191-235
- Sacks, L. V., Shamsuddin, H. H., Yasinskaya, Y. I., Bouri, K., Lanthier, M. L., & Sherman, R. E. (2014). Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000-2012. *Jama*, 311(4), 378-384.
- Sasinowski, F. J. (2012). Quantum of effectiveness evidence in FDA's approval of orphan drugs. *Drug Information Journal*, 46(2), 238-263.
- Sasinowski, F. J., Panico, E. B., & Valentine, J. E. (2015). Quantum of effectiveness evidence in FDA's approval of orphan drugs: update, July 2010 to June 2014. *Therapeutic Innovation & Regulatory Science*, 49(5), 680-697.
- Smith, J. F., Townsend, S. A., Singh, N., & Ma, P. (2012). FDA advisory committee meeting outcomes. *Nature Reviews Drug Discovery*, 11(7), 513-514.
- Steenburg, C. (2006). Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule, *The Food & Drug LJ*, 61, 295.
- Temin, P. (1980). *Taking your medicine*. Harvard University Press.
- Temple, R. J. (2003). Defining dose decrease. *Pharmacoepidemiology and Drug Safety*, 12(2), 151-2.
- Toma, S. V., Chiriță, M., & Șarpe, D. (2012). Risk and uncertainty. *Procedia Economics and Finance*, 3, 975-980.
- Wallach, J. D., Ross, J. S., & Naci, H. (2018). The US Food and Drug Administration's expedited approval programs: Evidentiary standards, regulatory trade-offs, and potential improvements. *Clinical Trials*, 15(3), 219-229.
- Wardell, W. M. (1974). Therapeutic implications of the drug lag. *Clinical Pharmacology & Therapeutics*, 15(1), 73-96.
- Wardell, W. (1978). A Close Inspection of the 'Calm Look'. *JAMA*, 239(19), 2004-2011.
- Wardell, W.M. (1978). The drug lag revisited: Comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976. *Clinical Pharmacology & Therapeutics*, 24, 499-524.
- Wardell, W. (1979). Rx: More Regulation or Better Therapies. *Regulation*, 3.
- Wardell, W. M., and L. Lasagna. (1975). *Regulation and Drug Development*. Washington, D.C.: American Enterprise Institute for Public Policy Research.

- Woloshin, S., Schwartz, L. M., White, B., & Moore, T. J. (2017). The fate of FDA postapproval studies. *The New England journal of medicine*, 377(12), 1114.
- Yudkin, J. S., Lipska, K. J., & Montori, V. M. (2011). The idolatry of the surrogate. *BMJ: British Medical Journal (Online)*, 343.



## Appendix I for Study 3: Tables

**Table I-1. Safety event reports received by year, FAERS**

Year	Safety reports	Serious outcome	(%)*	Deaths	(%)**
2006	335,629	230,389	69%	37,373	11.1%
2007	363,168	236,954	65%	36,878	10.2%
2008	439,167	270,617	62%	49,764	11.3%
2009	490,043	311,970	64%	63,925	13.0%
2010	672,489	389,682	58%	82,953	12.3%
2011	782,091	474,930	61%	98,942	12.7%
2012	933,104	539,434	58%	117,528	12.6%
2013	1,074,587	590,563	55%	116,822	10.9%
2014	1,203,970	682,865	57%	124,743	10.4%
2015	1,727,456	805,139	47%	148,752	8.6%
2016	1,691,764	832,127	49%	142,117	8.4%
2017	1,815,554	906,181	50%	164,079	9.0%
2018	2,156,854	1,109,481	51%	197,060	9.1%

[source: FDA FAERS Dashboard]

Notes:

\* the percentage of serious outcome of all reports;

\*\* the percentage of deaths of all reports

**Table I-2. Variable Descriptions**

Variables	Description
New/Supplemental	If new NDA/BLA, "new" If supplemental, "supplemental" If information not available, "n/a"
BLA/NDA	BLA, if BLA NDA, if NDA If information not available, "n/a"
BLA/NDA number	If not available, "n/a"
Drug descriptions - Brand name - Generic name - Sponsor - Drug class	Drug brand name Drug generic name (major active ingredient) Sponsor at the time of NDA/BLA review Therapeutic/disease class
Approval dates - Original approval date - Approval date	The original NDA/BLA approval date The approval date of supplement application

Variables	Description
Committee descriptions <ul style="list-style-type: none"> <li>- Committee name</li> <li>- Purpose of meeting</li> <li>- Center</li> <li>- Subcommittee</li> <li>- Joint committee</li> <li>- # of drugs discussed</li> </ul>	Full name, and abbreviation Brief description of the purpose of the meeting CBER or CDER Subcommittee (i.e. pediatric oncology) Joint with another committee The number of drugs discussed in a committee meeting  Note: The number of advisory committee meetings counts the number of agenda the committees discuss. If there are more than one drug per meeting and if these are asked with separate individual questions, they are counted separately. If two drug applications for one drug and the questions are separable, then I separated the meetings even if the number of postmarketing study mentioned shares the same number. But, in that case, I subtracted the double-counted numbers of mentions on postmarketing studies.
Meeting date	Advisory committee meeting date
Doc Type	If only minutes are available, "minutes" If transcripts are available, "transcript"
Approval	If approved, "yes" If not approved, "no"
Approval date	The date of approval by FDA
Chemical type	"NME" or "non-NME" If information not available, "n/a" (i.e. never approved)
Priority	"Priority" or "Standard" If information not available, "n/a" (i.e. never approved)
Orphan	"Orphan" or "non-Orphan" If information not available, "n/a" (i.e. never approved)
Accelerated	If information not available, "n/a" (i.e. never approved) If accelerated, "yes" If application was reviewed before 1992, "before 1992" If not accelerated, "no"
FDA questions <ul style="list-style-type: none"> <li>- Discussion questions</li> <li>- Voting questions</li> </ul>	# of discussion questions on approval # of discussion questions on benefit-risk # of discussion questions on postmarketing studies # of discussion questions on others # of voting questions on approval # of voting questions on benefit-risk # of voting questions on postmarketing studies # of voting questions on others <i>If information not available, "n/a"</i>
Voted	If the committee voted on approval or B/R profile, "yes" If the committee did not vote on approval or B/R profile, "no"
Unanimity	If unanimous, "yes" (excluding abstained votes) If not unanimous, "no" (excluding abstained votes)  Note: There are meetings where committees vote more than once. I prioritized more approval-relevant questions. If there were more than one approval-relevant voting questions, I put them in "unanimous" if there was at least one unanimous vote. I didn't count abstain votes when deciding unanimity.

Variables	Description
Vote results - # yes - # no - # total votes	The number of members who voted yes The number of members who voted yes Total number of votes including abstained
Vote concordance	Absolute value of the difference between yes and no votes divided by the sum of yes and no votes
% of votes approval	The percentage of yes votes of the total votes including abstained
Vote description (notes)	Notable, significant to report
PMS discussed	If discussed, "discussed" If not discussed, "not discussed" If PMS was mentioned more than 10 times throughout the transcript, "discussed substantially" when PMR/PMCs were discussed. But, I did not mark a case where the existing PM data were discussed as substantial discussion even if the word counts exceeds 10.
# of PMS mentions	The number of postmarketing mentioned in a meeting  Note: I searched and counted the following words: postmarketing, post-marketing, post marketing, postapproval, post-approval, post approval, postmarket, post market, post-market, surveillance, confirmatory, phase 4, and phase IV. I also searched the following words to identify any relevance to postmarketing studies where I could not find any of the keywords suggested above: further, future, additional, necessary, require, commit, and after approval. I didn't differentiate postmarketing from postmarketing studies because mentioning "postmarketing" could provoke a thought of "postmarketing studies" though it is debatable. I note the differences in discussion. If I separated the meetings even if the number of mentions on postmarketing studies shares the same number, I put the same number in each entry but I avoided double-counting when calculating the average number of postmarketing studies. Later I added "stage 4 or stage four or stage iv"
PMS discussion description	Contents of discussion on postmarketing studies
PMS-approval discussion	If postmarketing studies are discussed in the following contexts: (1) pre-approval vs. post-approval study (2) having postmarketing study is comforting (3) postmarketing study as a condition for approval (4) if approved, postmarketing study should be done I exclude confirmatory trial discussion on accelerated approval because the discussion is inherently about conditional approval.
# of PMR	(only for 2012-2016 drugs) The number of postmarketing requirements at the time of approval
# of PMC	(only for 2012-2016 drugs) The number of postmarketing commitments at the time of approval

Variables	Description
Efficacy evidence requirements	<p>(only for 2012-2016 drugs)</p> <p>(1) “conventional” if the requirement was traditional which is two adequate and well-controlled trials</p> <p>(2) “administrative flexibility” if evidence is consistent with some formal FDA system for exercising discretion</p> <p>(3) “case-by-case” if evidence is neither conventional nor administrative flexibility (orphan drugs sometimes get this exclusion).</p> <p>Note: I adopted Sasinowski (2012) and Sasinowski et al. (2014) classification methods. I also imported their data when applicable. For most part, I looked at drug approval package (clinical and statistical-efficacy review section, especially) where the FDA reviewers evaluate key clinical trials supporting the approval.</p>

**Table I-3. Advisory Committee Meetings by year and by committees**

Advisory Committee \ Year	1985	1986	1987	1988	1989	2012	2013	2014	2015	2016
Anesthetic and Analgesic	-	2	-	1	1	2	-	3	3	9
Anti-infective (Antimicrobial)	1	2	3	1	5	7	2	3	2	2
Anti-viral						2	2	-		
Arthritis	-	-	-	2	1	4	2	1	1	4
Bone, reproductive						2	3	3	1	2
Fertility, maternal	3	-	1	3	8					
Cardiovascular, Renal	1	4	5	5	5	3	2	8	1	-
Dermatologic, ophthalmic	-	-	1	1	1	2	-	1	2	1
Endocrinologic, metabolic	1	4	-	3	3	7	6	3	5	3
Gastrointestinal	3	4	1	2	2	3	1	-	-	1
Oncologic	3	2	2	3	3	8	5	3	5	4
Peripheral, central nervous	1	1	-	-	4	1	3	-	1	1
Psychopharmacologic	-	1	-	-	5	-	1	1	1	4
Pulmonary-Allergy	-	1	-	-	2	1	4	3	5	-
Total	13	21	13	21	40	42	31	29	27	31

Notes:

1. Medical Imaging Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, Pharmaceutical Science and Clinical Pharmacology Advisory Committee, and Pharmacy Compounding Advisory Committee are not included due to the nature of characteristics of their agenda and very small number of meetings held.
2. The Antiviral Drugs Advisory Committee was terminated in 2015 and all topics are brought to Anti-Microbial Committee (previously known as Anti-infective Committee). Bone, Reproductive, Urologic Drugs Advisory Committee (previously known as Reproductive Health Drug Advisory Committee) discusses topics that were discussed in Fertility and Maternal Health Drugs Advisory Committee.
3. Joint meetings were not double-counted. They were assigned to one of committees.

**Table I-4. The number of AC meetings where PMS-approval was discussed**

Committee	Period 1 (1985-1989)	Period 2 (2012-2016)
Antimicrobial	1 / 4 (25%)	2 / 11 (18%)
Cardiovascular and Renal	10 / 19 (53%)	2 / 12 (13%)
Gastrointestinal	1 / 11 (9%)	2 / 3 (67%)
Oncology	0 / 16 (0%)	2 / 14 (14%)

Note: committee meetings on accelerated approvals were excluded. This table shows the number of AC meetings (meeting-drug combination) not meeting agendas.

**Table I-5. The number of AC with PMS discussion, by application types**

Criteria		Period 1	Period 2
New vs. Supplement <sup>a)</sup>	New	27/43 (63%)	45/51 (88%)
	Supplemental	2/12 (17%)	5/8 (63%)
NDA vs. BLA	NDA	27/54 (50%)	38/47 (81%)
	BLA	2/2 (100%)	12/12 (100%)
NME vs. non-NME <sup>b)</sup>	NME	22/36 (61%)	35/41 (85%)
	non-NME	7/19 (37%)	15/18 (83%)
	n/a	0/1	-
Priority vs. Standard <sup>c)</sup>	Priority review	12/25 (48%)	28/28 (100%)
	Standard	16/25 (64%)	21/27 (78%)
	n/a	1/6 (17%)	1/4 (25%)
Orphan vs. non-orphan	Orphan	5/8 (63%)	22/24 (92%)
	non-orphan	24/48 (50%)	28/35 (80%)

Notes: Other expedited approval process (Breakthrough therapy, fast track, and accelerated approval) data is not included in this dataset because those programs were introduced after 1990. Breakthrough therapy was instituted in 2013, fast track in 1998, and accelerated approval in 1992 respectively.

- a) One meeting has both new drug application and supplemental application in Period 1.
- b) Information is not available for 1 drug application in Period 1. NME and non-NME distinction is valuable only for new drug applications. Information on PMS discussion for 1 application was not available in Period 1.
- c) Data on 5 drugs (6 meetings) in period 1 and 4 drugs in period 2 are not available for review type.

**Table I-6. Vote concordance**

	Period 1	Period 2
with PMS discussion	0.76	0.74
without PMS discussion	0.78	0.75
with substantial PMS discussion	0.93	0.74
without substantial PMS discussion	0.76	0.75
with PMS-approval discussion	0.68	0.52
without PMS-approval discussion	0.88	0.79

Note: the sample is all advisory committee meeting agendas where committees voted. Vote concordance = Absolute value of difference between yes and no / sum of yes and no votes. Absent votes were not counted. If the votes were unanimous, the vote concordance is 1.

**Table I-7. Characteristics of drugs discussed in ACs**

<i>Characteristics</i>	<i>Period 1 (1985-1989)</i>	<i>Period 2 (2012-2016)</i>
Total number of drugs	44	46
New drugs (number, %)	35 (80%) <sup>1</sup>	40 (85%)
NMEs (number, %)	27 (61%) <sup>2</sup>	31 (78%)
Priority review (number, %)	21/39 (54%) <sup>3</sup>	20/43 (47%) <sup>4</sup>
Orphan (number, %)	<b>7 (16%)</b>	<b>20 (43%)</b>
BLAs (number, %)	<b>2 (5%)</b>	<b>12 (26%)</b>

Notes:

1: in Period 1, there is a drug both with new and supplemental approvals (the drug was discussed twice in Period 1). Also, there is a drug that was discussed for original approval and then supplemental approval in period 1.

2: in Period 1, information on whether a drug was NME or not was not available for 1 drug, and 1 drug has both NME and non-NME because the drug was discussed twice (first new drug application, and then supplemental).

3: in Period 1, information on whether drug applications had priority review was not available for 5 drugs. And, 1 drug had a non-priority review and unknown review status because the drug was discussed twice in Period 1 (first new application, and then supplemental)

4: in Period 2, information on whether drug applications had priority review was not available for 3 drugs

Table 3-11 in Appendix I shows the characteristics of drugs discussed in advisory committee meetings in Period 1 (1985-1989) and Period 2 (2012-2016). More new drugs and NMEs were discussed in Period 2 than in Period 1. The percentage of drugs with priority review was higher in Period 1 than in Period 2. A significant difference was observed in orphan drugs and biologics: substantially higher percentage of drugs discussed in committee meetings in Period 2 are orphan drugs and biologics. But it can also be explained by the fact that more orphan drugs and biologics were approved during 2012-2016 compared to the period of 1985-1989. During

1985-1989, 39 orphan drugs were approved while 196 orphan drugs were approved during 2012-2016. And, Biologics-based drug approvals also increased significantly in the 2010s compared to the 1980s.

**Table I-8. Final decisions made by the FDA, among 24 drug approvals with PMR/PMC discussion**

PMR and PMC	7
PMR	5
PMC	1
PREA only	5
No PMR/PMC	2
Approval rejected	5

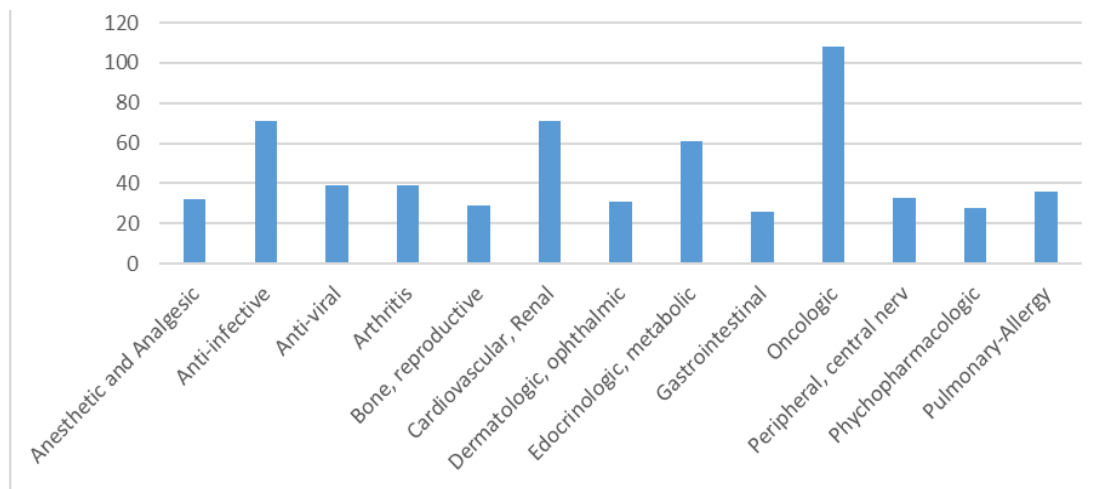
Out of 46 drug approvals in period 2, committees discussed postmarketing studies (recommending postmarketing studies) in 25 drug approvals, excluding accelerated approvals. Of the 25, the following is the final decision made by the FDA:

Out of 25, 13 drugs (52%) ended up with postmarketing requirements and/or commitments other than PREA. Five drugs had only PREA studies that were not discussed. Two of them had no requirement/commitment.

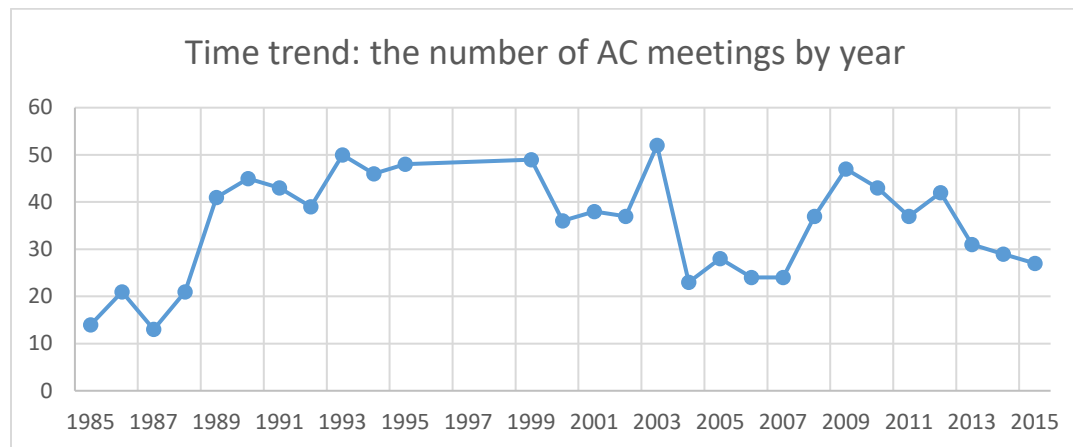
## Appendix J For paper 3: Figures

See Figure 2 in Kesselheim, A. S., Wang, B., Franklin, J. M., & Darrow, J. J. (2015). Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ* 2015;351:h4633

**Figure J-1. Time trend: All expedited drug approvals, 1987-2014**



**Figure J-2. The number of AC meetings by disease class (2000-2015), all ACs except for medical imaging products advisory committee**



**Figure J-3. Number of Advisory Committee meetings (1985-2015)**



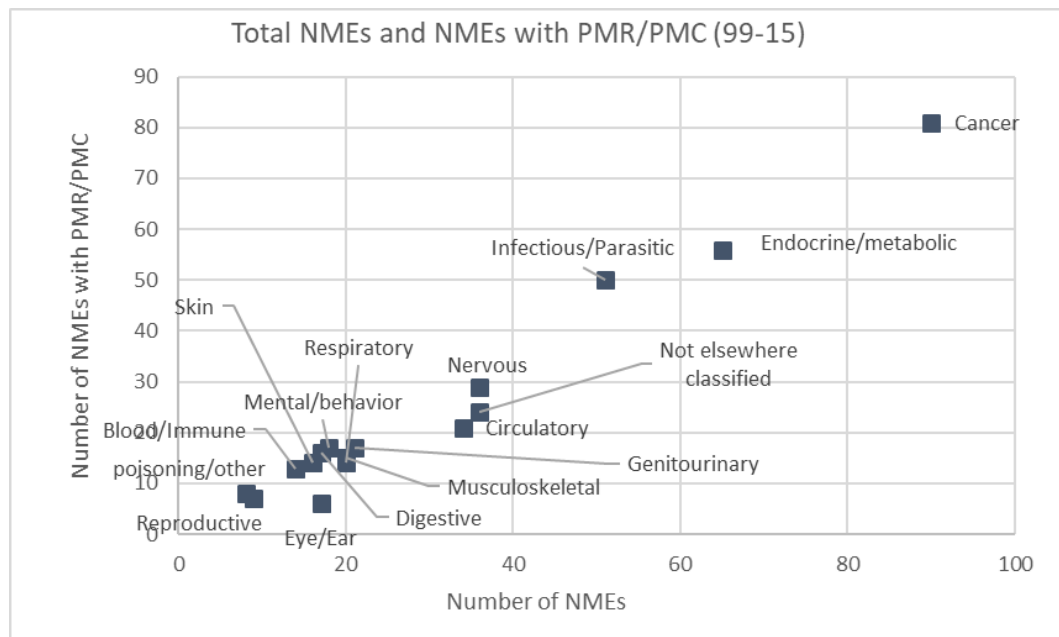
See Figure 2 in Smith, J. F., Townsend, S. A., Singh, N., & Ma, P. (2012). FDA advisory committee meeting outcomes.

**Figure J-4. Ad Com recommendations and FDA approval decision**

Note: The sample includes advisory committee meetings that include votes for or against drug approval during 2001-2010.

See Figures in <https://www.3dcommunications.us/insight/current-trends-in-fda-advisory-committee-member-practices-and-preferences-a-survey-on-what-cder-panel-members-say-influences-them/>

**Figure J-5. Ad Com recommendations and FDA approval decision**



**Figure J-6. Total NMEs and NMEs with PMR/PMCs by therapeutic areas (1999-2015)**

## Appendix K for Study 3: Interview Data – Key comments

### Advisory Committees

Interviewee #2 (2013, 2016 meetings): FDA delivered clear message “if this is approved, we are going to be receptive of PMS.” That message signaled that the sponsor is going to do PMS. If there was going to be no additional data collection, the committee would have been more reluctant to recommend it. Approval decision making would be different for supplemental compared to new drug approval. The bar can be higher for supplements because it is all about marketing (the drug is already available). *Recognized the role of PMS on approval*

Interviewee #3 (current member): PMS doesn’t affect approval decision that much. We focus on efficacy and safety data at hand to decide whether we are going to recommend it or not. It may be very different for cancer drugs. We never even think about marketing. We look at the data we have. It would be unusual if PMS gets in the middle of approval process—the data has to suggest. *No or limited role of PMS*

Interviewee #4 (2011, 2013 meetings): Drug availability issue is crucial for approval decision. If other drugs were available, I would have not approved the drug based on the data provided. Even if they said there will be no PM Studies, I would still recommend approval because of drug availability. PMS is not a greater factor than “demand” for a drug. And, the interviewee adds: “not only long-term safety but also long-term efficacy matters. If a drug stayed long in the market, I wouldn’t worry about safety too much. Do I know all possible toxicity? No, but it won’t hold approval.” *No or limited role of PMS*

Interviewee #12 (2005-2007 meetings, currently working to launch a product): The effect of PMS on approval process may vary depending on whether it is small population without alternatives such as orphan drug, transplant drug, etc. People may be more willing to approve drugs when target population is small without alternatives such as orphan drugs. Also, company's claim that PMS will be done will have more weight if they lay out the detailed plans. If a sponsor suggests a very detailed plan, that assures the committee. But, overall, it is a grey area. ***Recognized some role of PMS, but unclear under what circumstances it may happen***

Interviewee #13 (current member): Postmarketing studies are valuable especially when addressing unanswered questions. For recommending approval of individual drugs at the meeting, it would be great to have more data, but you have to decide on the data at hand. FDA genuinely want to understand...they are more into discussion rather than votes per se. In his discussion during the meeting, he said that "I voted yes as a pediatrician when this study was really done primarily in a geriatric population, and my yes is probably not an unconditional yes, but we didn't get to limit our recommendation other than to say how we might like to see it used or what might be on the product recommendation." Also, "in part because there is not a lot of good alternatives. I urge and beg the sponsor to do additional studies, particularly in the pediatric population, and to take what we've learned by our input, your input, the FDA's input, and try to perfect those studies, and to do additional phase 4 studies." Approving new drugs should be stricter. And, some studies are not done well (e.g. Chantix) and motivation to do well is really low after approval. ***Unclear role of PMS***

### **FDA reviewers**

Interviewee #6: Not so much in this division. We want to be certain B-R balance. Heart failure trials have thousands of patients, for example, and we have pretty good safety profile. It could happen more in the future when we approve drugs for smaller population. But I think it is happening in anti-viral and oncologic drugs. I have a theory on Anti-viral and Oncologic drugs: they are under huge pressure to approval drugs early on. I think people are willing to approve drugs with less data (maybe less about safety studies, but more about routine studies like pharmacological explorations can wait until approval). So whatever data are available in the first application can be used to determine approval if they feel it is enough and the rest can be examined after approval. But I recommend that you talk to other divisions. ***Some role of PMS on approval in certain drugs***

Interviewee #7: I don't think we approved drugs that would not have been approved without PMR/PMCs. It is hard to tell the effect of PMS on accelerated approval. We don't have many symptom-treating drugs—i.e. steroids or NSAIDs—in this division. On safety side, it is much less clear. We don't have many PMRs in this division compared to metabolic and endocrinology drugs, GI-meds, and pain medications that have increasing PMR/PMCs. The 2009 guidance “Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” is an example: that guidance has required large cardiovascular outcomes trials for all new type 2 diabetes drugs. ***No role of PMS***

Interviewee #8 (working in rare disease drugs): It happens a lot that the availability of PMR/PMCs make it possible to recommend approval of an NDA which might otherwise be delayed until more pre-approval information became available. Almost all rare disease drugs are

accelerated approval. For the last ten years most rare disease drugs got PMR/PMC strings.

***Recognized role of PMS for rare disease drugs***

Interviewee #10: Having the option of PMR/PMCs affecting approval happens – but it is difficult to quantify it. ***Recognized role of PMS***

**Industry**

Interviewee #1: Approval is supposed be contingent on PMR/PMCs but the problem is toothless enforcement. In general, pharma companies are afraid that FDA would delay approval, FDA would not give you a longer exclusivity, and FDA would withdraw their products. All incentives work for keeping the drug in the market. Potential bad results of PM studies are risk for firms. ***Unclear role of PMS***

Interviewee #5\*: Anyone will say the priority is patient safety – all of us are working toward the same end and in that sense PMS is important (this interviewee was particularly careful about what goes on record and what will be published from his/her comments). No direct mention about the effect of PMS on approval decision making process. ***Not much insight***

\*: data from this interviewer is not included in the analyses because this interviewer didn't have much experience with the FDA and postmarketing studies.

Interviewee #9: Trades between approving drugs faster with PMS and delaying approval happen. It is unreasonable to think it doesn't happen. FDA is under pressure to approve drugs fast and given the pressure, FDA mandates PMRs so that it can make right decisions (fix it later if something wrong found or make sure their approval was well founded). No one pays attention to

carry out PMR/PMCs—companies agree to almost anything to get their drug approved. Enforcement and compliance is not good. ***Recognized role of PMS***

Interviewee #11: PMR/PMCs are there because FDA is speeding up the approval. Look at orphan drugs: 81% of orphan drug approved based on 1 trial – for common disease, typical two. Look at accelerated approval.

## Appendix L for Study 3: Interview Questions

### **Group 1. FDA Reviewers**

#### General

1. Could you briefly tell me your roles and responsibilities related to postmarketing studies at the FDA? Please describe the process of your work related to postmarketing studies.

#### Establishing PMR/PMCs

2. How do you decide whether a known or an unknown serious risk should be studied?  
What is the process of decision making and who are involved? When do you consider safety PMR/PMCs instead of REMS, and vice versa?
3. Could you describe how you determine whether a safety study should be required or requested? In other words, how do you determine whether you would invoke FDAAA 2007?
4. Is there a formal or informal process where you determine whether a postmarketing study is needed for drug approval? Please describe the process including who initiates the process and the timing of discussion. Is there formal schedule?
5. How and under what circumstances do you establish PMR/PMCs for drugs already in the market? How is the process different from the process of establishing postmarketing studies before approval?

#### Concept of the PMR/PMC option

6. Given much more postmarketing studies compared to 20-30 years ago, do you think the PMR/PMC option is more available in drug approval decision making process?
7. When you have to negotiate (all PMCs), would companies agree to as many as studies they have to do? If they do agree PMCs, are you as confident as PMRs they would carry out?

Use of Advisory Committees (less important)

8. Under what circumstances, is a NDA/BLA referred to the advisory committee?
9. How do you determine whether a discussion of postmarketing studies should be included in the meeting agenda and voting questions? Who determines the discussion agenda and by what criteria?

Impact of PMR/PMCs on the approval process

10. Can you give me an example of where you had to decide between approval with PMR/PMCs and delaying approval? What “conditions” would make you more willing to approve drugs with serious risks rather than delaying approval?
11. Can you identify any cases where the FDA recommended a drug approval with PMR/PMCs, the drug that would not have been approved without PMR/PMCs? Do you think PMR/PMCs make a drug approval decision easier?
12. Let’s suppose there is a NDA that has slightly unfavorable benefit-risk profile compared to other drugs in the class. If you know that postmarketing studies will be carried out and generate more safety data after approval, would you more likely to approve the drug? If



you are not sure whether postmarketing studies will be carried out and generate safety information in the postmarketing settings, would you make a different decision?

13. If there is no impact of PMR/PMCs on the approval process, why would FDA requires such studies or pursues them?

Further improvement

14. From your perspectives, what do you see can be improved in the drug approval process and the use of postmarketing studies?

### **Group 2. advisory committee**

General

1. Can you please briefly describe your position and a little bit of background as well as your experience with FDA? And if you have any postmarketing studies?

AC meeting process and voting

2. When do you get to know the voting questions? How often did you generally agree with the questions set by the FDA? If you don't agree the set of questions provided by FDA, what would you do? What can you do?
3. If FDA does not provide questions on PMR/PMCs, would you still consider PMR/PMCs as an option? Would you know what kinds of postmarketing studies were required or committed even if the issues of postmarketing studies were not brought to the committee meetings? How?

4. Do you think some PMR/PMCs are inappropriate? Why?

The availability of postmarketing study options

5. Have you ever brought it up when FDA didn't? Have you seen cases where advisory committee members initiated discussions about PMR/PMCs when the option is not offered by FDA or firms?
6. In the advisory committee meeting you attended, FDA or firms did not mention anything about PMR/PMCs. What do you think it means?
7. In the advisory committee meeting you attended, FDA did ask the committee vote on PMR/PMCs, how did you feel their question is adequate?
8. What is your general perception about the availability of postmarketing data/information on drugs today (compared to pre-FDAAA 2007)? In other words, do you feel more confident that FDA will collect postmarketing data after FDAAA 2007 with "requirement"?

Impact of PMR/PMCs on approval

9. Can you describe your thought process of decision-making if a drug should be approved with PMR/PMCs or approval should be delayed? What are the criteria for such decision? Under what circumstances, would you vote for approval with PMR/PMCs and not delay approval?
10. In a meeting, you said "I would vote for yes, but postmarketing studies should be required" Did you mean that you would not approve the drug otherwise?

11. Can you share any cases where a drug was approved with PMR/PMCs, the approval that would not have been favored without PM studies? What do you think about the decision?
12. Let's suppose that a NDA shows slightly unfavorable benefit-risk profile compared to other drugs in the same class. If you know that postmarketing studies will be carried out and generate more safety data after approval, would you vote for approval? If you are not sure whether postmarketing studies will be carried out and generate safety information in the postmarketing settings, would you make a different decision?
13. Do you feel in general that the PMR/PMC options affect approval process? How?

### **Group 3. Pharma Companies**

#### General

1. Can you please tell me your current position and a little bit of background on your experience with FDA?
2. How is your job related to postmarketing studies? Could you tell me background on your experience with FDA on postmarketing studies?

#### Approval process

3. What factors do you think affect the approval process other than the benefit risk profile of a drug? Or what factors do you think affect the interpretation of benefit-risk profile?
4. Why do you think some cases are referred to AC meetings while others are not?
5. Do you think, by and large, NDA/BLA review process has been getting faster and more efficient? Why do you think it's getting faster and more efficient?

6. Then what about the standard of proof? Do you observe changes in the standard of clinical trials and evidence that FDA seeks? Since when? What trends do you observe in FDA's seeking evidence on drug's safety and efficacy pre-approval?

#### Development of postmarketing studies

7. When do you usually notice the need for postmarketing study in drug development process?
8. When do you usually first talk about postmarketing studies with FDA? Is the conversation on postmarketing studies usually initiated by FDA or by sponsor?
9. How often do you speak with FDA staff regarding postmarketing studies?
10. Could you please describe the negotiation process on postmarketing studies with FDA?
11. How do you feel about the appropriateness of FDA's suggestions for PMR/PMCs on the whole? i.e. size of study, length of study, endpoint, etc.
12. Could you share your experiences on both cases: (1) FDA's suggestion was appropriate; (2) FDA's suggestion could have been better? And in (2) case, how did you deal with it?

#### Voluntary studies vs. PMR/PMCs, Compliance

13. How different are your voluntary studies from PMR/PMCs by nature? Are there any overlaps?
14. How different are PMRs from PMCs? Is there a systematic difference in terms of conducting such requirements and commitments? In what ways?
15. Would a requirement be taken more seriously compared with a commitment?
16. What are the difficulties of conducting PMR/PMCs in time?

17. When your drug faces a market competition, would you still carry out PMR/PMCs?
18. When you consider drug discontinuation, would you still carry out PMR/PMCs?
19. When you do consider terminating a study? Under what circumstances are PMR/PMCs being delayed?
20. Under what circumstances would you prefer terminating PMR/PMCs? Even at the risk of monetary penalties and/or losing FDA's trust on your firm?
21. If you consider not conducting PMR/PMCs, how would you approach initiating conversation with FDA?

#### Impact of PMR/PMCs on approval process

22. Can you describe your understanding of FDA's decision thought process on whether a drug should be approved with PMR/PMCs or approval should be delayed? What do you think their criteria are for such decisions?
23. What "conditions" would make FDA more willing to approve a drug with a serious risk rather than delaying approval? How are those conditions different depending on whether the risks are known or unknown?
24. Can you share any cases where FDA approved with PMR/PMCs, the approval that would not have been favored without PMRs?
25. Have you seen any cases where committees did not vote for favorable benefit-risk profile but voted for approval with PMR/PMC options? Could you describe such cases?
26. Let's suppose that a NDA shows slightly unfavorable benefit-risk profile compared to other drugs in the class. If FDA and advisory committee members know that postmarketing studies will be carried out, do you think they would more likely to

approve/vote for approval? If they are not sure whether postmarketing studies will be carried out and generate safety information in the postmarketing settings, do you think they would make a different decision? Could you explain your thoughts?

27. Do you feel in general that the PMR/PMC options affect approval process? How?

28. If there is no impact of PMR/PMCs on the approval process, why would you agree to PMR/PMCs?

## Appendix M for Study 3: Committee Comments on PMR/PMC-approval discussion

(Table 3-4 in Section 3.4.2 provides brief contents of discussion on postmarketing studies)

**Table M-9. More detailed comments on PMS-approval discussion from the committee meetings**

Committee	Year	Drug name	Comments
Cardiovascular	1986 (3/27)	Lidoflazine, NDA, non- expedited	<p><b>There were concerns about post-approval regulatory actions when things fall out in the postmarketing settings. There were discussions on postmarketing studies, but the role of PMS on approval decision was not significant. The committee wanted to see more data and study results before recommending approval. Votes: 0 yes, 8 no</b></p> <p><b>Approval: rejected by the FDA</b></p> <p>Dr. Morganroth (Sponsor): Also postmarketing surveillance is another opportunity to look at that issue. (p.211)</p> <p>Dr. Wildnauer (Sponsor): ...as Joel (Morganroth) mentioned, in postmarketing surveillance, .... these risks can better be defined, and at the same time provide ultimate therapy for the treatment.. (p.213)</p> <p>Dr. Epstein (external consultant, no voting right): One could at least infer from that there is a good possibility that, therefore, this drug will be active in patients who are not responsive to the more traditional categories of drug. There is no evidence that the company has presented that this is, in fact, the case. I do not know what the rules of the FDA are relating to that. It may be that the company should be required to show that this laboratory demonstration of a new class of drug, a non-calcium-channel/ calcium-entry blocker, is effective in patients who have been shown to be refractory to traditional antiarrhythmic agents. If that is the rule, then so be it..... But to me this is a very exciting drug, because it is a new class of drug that has been shown to have antianginal efficacy....I would certainly lean towards giving it approval, with major limitations.... I think that drug should be available... (p.220-221)</p> <p>Dr. Pitt (committee, <b>voted no</b>): I think we would all await your studies and other studies showing that. It sounds like this is a very interesting drug, but I think without the data one can get misled..... (p.221)</p> <p>Dr. Epstein (external consultant, no voting right): This drug should be made available. In parallel, there could be clinical trials to determine whether, in fact, this drug is efficacious. (p.222)</p> <p>Dr. Lipicky (FDA): What if, when the clinical trials went on in parallel, they found that, in fact, it did not work in that population? What would you do then? Let's say the scenario falls out that, in order to make this thing be available, one made it available and trials went on in parallel, postapproval, and the trials found it did not work in the population indicated. Then what would you do? (p.222)</p>

Committee	Year	Drug name	Comments
			<p>Dr. Epstein (external consultant, no voting right): The logic of that would be that it would be withdrawn. if it is not effective and it is dangerous then we would have to it. (p.223)</p> <p>Dr. Goldstein (committee, <b>voted no</b>): ...although it is uniquely effective ... it is uniquely risky. I think it is very hard to anticipate how these data will go. (p.224)</p>
Cardiovascular	3/27/1986	Vascor/ Bepridil NDA #19002 NME, Priority	<p><b>More data would make the FDA and committee able to weigh the balance between benefit and risk. Two committee members indicated that the drug should be available with limited use and the likelihood of getting meaningful data premarketing is same as the likelihood of getting data postmarketing. The other six members still voted no for recommending approval. There was little to no role of PMS on approval observed.</b></p> <p><b>Votes: 2 yes, 6 no</b></p> <p><b>Approval: 4.75 years delayed. Approved on 12/20/1990<sup>229</sup></b></p> <p>Dr. Fisher (committee, <b>voted yes</b>): My feeling is -- it should probably be approved, but with a lot of restrictions the patient populations and a clear statement of the uncertainties.... But do we have to hold up a drug every time we would like studies in a different population than the one the company chose to study? (p.130-131)</p> <p>Discussions on both bepridil and lidoflazine</p> <p>Dr. Kowey (committee, <b>voted no</b>): I would prefer to see more data in regard to some of the things that we spoke about with bepridil..... I do not think that, given the fact that we do not have that kind of information, I feel very comfortable in making recommendations about its use. I am not sure why those patients died..... In view of that kind of information, I feel very uncomfortable about recommending approval at this time, under any circumstances. (p.232)</p> <p>....</p> <p>Dr. Fisher (committee, <b>voted yes</b>): I think the drug should be approved , with certainly more restrictive sorts of labeling than are available for many anginal drugs..... unless it is really an extreme case, I do not feel that I can be responsible for the behavior of the medical community, should the medical community choose to ignore the labeling. It seems to me that that is a separate issue which relates to malpractice and medical sociology, and all sorts of things that, by and large, are beyond the scope of this committee. (p.233)</p> <p>Dr. Woosley (committee, <b>voted no</b>): I would feel much more comfortable if there was something showing better than what is out there, to justify the risk of putting QT, no matter what that means. If it is good, tell us that it is good. If it is bad, tell us how bad, and tell us something to counterbalance that. That's my problem with the whole</p>

<sup>229</sup> Vascor's NDA was filed in December 1983. The drug's progress through the review process was apparently thwarted in 1986, when FDA's Cardio-Renal Drug Advisory Committee voted not to recommend approval for Vascor because of safety concerns. To support approval, the committee requested data showing some advantage over other anti-anginal agents. (Pink Sheet, January 1991)

<https://pink.pharmaintelligence.informa.com/PS018592/FDA-APPROVES-23-NEW-MOLECULAR-ENTITIES-IN-1990-FOR-SECOND-YEAR-IN-A-ROW-NDA-REVIEWS-TOOK-AN-AVERAGE>



Committee	Year	Drug name	Comments
			<p>situation. I just do not have enough information to assess the risk/benefit ratio.... (p.233)</p> <p>DR. TEMPLE (FDA): If it were not for the arrhythmia study -- say it was never done, which they might well not have done -- would this conclusion still be the same, entirely because of the QT prolongation? That is important because someone could do another arrhythmia study and find no such five to nothing -- is there any point in doing that? .....(p.234)</p> <p>.....</p> <p>DR. GOLDSTEIN (Committee, <b>voted no</b>): But given the QT interval data, wouldn't it be appropriate to demand that something like the VED trial went on? In retrospect, even though maybe from a financial point of view it is unfortunate the trial was done, from an approval point of view, it seems to me mandatory. (p.236)</p> <p>DR. FISHER (Committee, <b>voted yes</b>): I assume, if they redo the VED trial and there is a survival deficit to the drug, then it would not be approvable. Is that correct? (p.236)</p> <p>DR. TEMPLE (FDA): That is not what I hear. ... you see a disadvantage -- not absolutely proved, but certainly suggested, and present on theoretical grounds -- and no clear advantage....I hear you saying that there are two things that could get people out of this. One, if the arrhythmia study was redone and showed nothing, the balance would then tilt toward -- there is a suggestion.....Alternatively, clear evidence that in people who do not respond to other agents or who do not tolerate them that this is a drug that can treat people with bad angina -- either of those things might tilt the balance. (p.236-237)</p> <p>.....</p> <p>DR. PITT (Committee, <b>voted no</b>): I think, if the VED study were done again or completed and came out with placebo having more deaths or equal deaths, then. we would have another drug with no risk, and I guess we would have to say that -- (p.238)</p> <p>DR. LIPICKY (FDA): How many people would vote that it is not now, on the basis of current data, approvable?..... Six to two. ....We heard Dr. Fisher. Dr. Margolius, why would you have voted that way? (p.239)</p> <p>DR. MARGOLIUS (Committee, <b>voted yes</b>): I feel reasonably certain that the likelihood that you are going to generate the kinds of data that are going to be full of clarity and satisfy all the uncertainties about the symptomatic treatment of arteriosclerotic disease and angina, intractable angina, in the kinds of patient populations that we are talking about -- they are not likely to appear in front of us. The notion of approving it, with restrictions in labeling and caution and provisos and inhibitions, is as likely to result in the generation of meaningful data about its disadvantages and advantages as not approving it. (p.240)</p>
Cardiovascular	1986 (3/28)	Hytrin/ Terazosin, NDA, NME, non- expedited	<p><b>There were concerns on doss-related, hematologic, and tumorigenic issues. The committee discussed that postmarketing should be followed, but the concern is not sufficient to withhold approval. The role of PMS on approval was unclear.</b></p> <p><b>Votes: 9 yes, 0 no</b></p>

Committee	Year	Drug name	Comments
			<p><b>Approval: 1.5 years delayed. Approved on 8/7/1987. It is unclear what additional data the sponsor had to prepare for the NDA for 1.5 years.</b></p> <p>Dr. Pitt (Committee, <b>voted yes</b>): Are there clinical data which would clearly take advantage of that property? It sounds like, if not, one should be doing those studies. (p.146)</p> <p>.....</p> <p>DR. BORER (Committee, <b>voted yes</b>): What kind of information do you want to be provided for us to be able to determine that that is a problem that would warrant not approving the drug? (p.II-43)</p> <p>....</p> <p>DR. MARGOLIUS (Committee, <b>voted yes</b>): I think it is going to be the interest of the sponsor and the interest of the Agency to explore that and become comfortable with those changes, either by virtue of package insert information or additional examination of postmarketing data, whatever you decide you want to do. I don't think you should just sort of let that go by. (p.II-44)</p> <p>.....</p> <p>DR. PITT (Committee, <b>voted yes</b>): I was just going to support Harry (Dr. Margolius)'s statement that perhaps some statement in the labeling that this occurs would alert people to be looking for this and perhaps postmarketing surveillance would be all that one would do at that point. (p.II-44)</p> <p>DR. BORER (Committee, <b>voted yes</b>): All right. With regard to the dose response issue, do you think that it is of sufficient concern to warrant withholding approval at this time or is this also something that can be dealt with? (p.II-45)</p> <p>DR. FISHER (Committee, <b>voted yes</b>): No, my plan is to vote for approval, unless I hear something I haven't heard yet. I mean the FDA is here and I have a lot of faith in the people that they will at least go back and look at the data to satisfy themselves. (p.II-45)</p> <p>DR. BORER (committee, <b>voted yes</b>): ...do we recommend approval of terazosin for the use in management of hypertension? (Show of hands) Okay, unanimously it is recommended for approval in the management of hypertension. (p.II-45)</p> <p>.....</p> <p>Dr. Borer (Committee, <b>voted yes</b>): We believe that it is appropriate that postmarketing studies should be performed... (p.II-52)</p> <p>.....</p> <p>DR. MARGOLIUS (Committee, <b>voted yes</b>): Then the other issue is relation to the hematologic things. There is no question about that. (p.II-53)</p> <p>DR. BORER (Committee, <b>voted yes</b>): So you would want the postmarketing study to at least reassure one -- (p.II-53)</p> <p>DR. MARGOLIUS (Committee, <b>voted yes</b>): Absolutely. It is just a matter of not getting blind-sided here. (p.II-53)</p> <p>.....</p> <p>Dr. Temple (FDA): ...what you have here maybe is fairly common, very small effects. What you are worried about probably is rare, large effects. We don't know any way to look for those except by watching</p>

Committee	Year	Drug name	Comments
			<p>carefully over reports. Now, are you advocating something in addition to that? Further studies of the small effects? Before we go asking for a study we need to know what you think would be useful...(p.II-54)</p> <p>DR. TEMPLE (FDA): And our experience has been that once you put it in the label and sort of flag it for people, there isn't any better way to find out about it than to watch the reports as they come in....But the alternative is to ask for some follow-up study of 10,000 people, or something.... (p.II-55)</p> <p>DR. MARGOLIUS (Committee, <b>voted yes</b>): ... I don't know how you demand that or in what population of patients.....I just can't tell you what I would do but I know I would gather more information.... (p.II-55-56)</p> <p>DR. TEMPLE (FDA): That is fine. I think we understand. We need to see if there is a mechanism that can be explored. (p.II-56)</p> <p>DR. MARGOLIUS (Committee, <b>voted yes</b>): Yes. (p.II-56)</p> <p>Dr. Borer (Committee, <b>voted yes</b>): Okay, so we are amending our recommendation from a postmarketing study to a premarketing FDA thorough investigation of the data to see if there is any reason for concern. (p.II-56)</p> <p>...</p> <p>Dr. Borer (committee, <b>voted yes</b>): ...We are recommending some stated concerns and a suggestion specifically for an evaluation of the low end of the dose-response curve with and without concomitant therapy. (p.II-56)</p>
Cardiovascular	1986 (9/29)	Brevibloc/ Esmolol, NDA #19386, NME, Priority	<p><b>The committee talked about additional data, and specifically whether they want the data before the approval (whether the data is necessary for approval). There was informal voting, and 4 out of 7 voted for approvability. But they reached a consensus unanimously on the need for FDA to review some data before approval. The role of PMS is unclear.</b></p> <p><b>Votes on approvability (general): 4 yes, 3 no</b></p> <p><b>Approval: approved on 12/31/1986 with a postmarketing commitment on the hypotensive effect of this drug. Esmolol was approved for the acute, temporary control of ventricular rate in certain supraventricular arrhythmias such as sinus tachycardia and atrial flutter and/or fibrillation in the perioperative, postoperative, or emergency setting.</b></p> <p><i>Discussions on the initial indications: coronary-artery, perioperative tachycardia and hypertension</i></p> <p>Dr. Pratt (committee, <b>voting unknown</b>): If this drug is to be approved for some type of prophylactic approach, then I think there should be an endpoint outcome study.....One could look at esmolol, if it really is of a therapeutic benefit, to see if it is better than standard therapy in preventing some of the ischemic episodes. And I think that would be a possible study that could be done. And if it is to be approved for a prophylactic issue, I think it should be done. And I think that that should weigh fairly heavily in a decision about prophylaxis.</p> <p>....</p> <p>Dr. Borer (committee, <b>voted yes</b>): ...it sounded from what we heard from the consultants that it would be difficult, if not impossible, to</p>

Committee	Year	Drug name	Comments
			<p>mount the kind of study that we would all like to see in order to verify the appropriateness of using a drug like this....</p> <p>....</p> <p>Dr. Borer (committee, <b>voted yes</b>): Fine. Then it is impossible to do. Do we need that kind of information to be able to approve the drug? Is there anybody who believes we must have that in order to approve the drug? (p.104)</p> <p>DR. FISHER (committee, <b>voted no</b>): I mean, to me, it does depend on the feasibility. (p.104)</p> <p>Dr. Borer (committee, <b>voted yes</b>): Well, let me say that you can vote no...(p.105)</p> <p>DR. PACKER (committee, <b>voting unknown</b>): ....I don't mind, Ray, being anything that we would do now but I think we would be a little bit reluctant to approve a drug for treatment of silent ischemia based purely on its abolition of Helter changes, without further evidence about what they meant. But as long as we can be inconsistent, then to vote now is no problem. (p.105)</p> <p>DR. BORER (committee, <b>voted yes</b>): But that is not -- we are not talking about methods of study now. We are just talking about what it is that we require..... (p.105)</p> <p>.....</p> <p>Dr. Borer (committee, <b>voted yes</b>): But do we have a consensus that that is necessary information before we can consider approval of this drug? (p.107)</p> <p>DR. KOWIE (committee, <b>voting unknown</b>): Yes (p.107)</p> <p>DR. BORER (committee, <b>voted yes</b>): Carl, do you think that it is necessary to have some objective evidence from a reasonably controlled trial that ischemia is minimized or reduced? (p.107)</p> <p>....</p> <p>Dr. Borer (committee, <b>voted yes</b>): Well, it sounds as if there are ...four of seven voting members here who have said that some evidence of prevention of ischemia in, presumably, a placebo controlled trial would be necessary for consideration of approvability of this drug, if it were going to be given as a prophylactic agent. (p.111)</p> <p>....</p> <p>Dr. Borer (Committee, <b>voted yes</b>): ....In other words, is there a group of patients who don't need the studies in order for the drug to be approved? (p.121)</p> <p>.....</p> <p>Dr. Leier (Committee, <b>voted yes</b>): Yes, I think that population exists. (p.124)</p> <p>Dr. Borer (Committee, <b>voted yes</b>): And would you be willing to approve the drug for use in that population if we could agree on defining it, even before other studies showing ischemic efficacy have been performed? (p.124)</p> <p>....</p> <p>Dr. Leier (Committee, <b>voted yes</b>): Yes, .... (p.124)</p> <p>DR. BORER (Committee, <b>voted yes</b>): ... So far it seems that there is a small majority favoring the concept that there must be some additional data about efficacy before the drug can be approved for</p>

Committee	Year	Drug name	Comments
			<p>use before induction. Let's put that to a final vote...How many people believe that we cannot consider for approval this drug for any subgroup of patients unless we have some additional data that we don't have now [as a pretreatment]? Three [out of seven]. (p.133)</p> <p>.....</p> <p>DR. BORER (Committee, <b>voted yes</b>): How many believe that we can define a group of patients in whom it would be reasonable to approve the drug now as a pretreatment, even before we have additional information about efficacy, whatever that additional information about ischemia might be? How many believe that we can approve the drug? Okay, that is four [out of seven]. A little bit of change. So we now have a majority favoring the idea that there is a group of patients..... (p.133)</p> <p>.....</p> <p><i>A strong opposition from Dr. Lipicky (FDA) and a committee member came against the comment that they could approve the drug even without additional data.</i></p> <p>.....</p> <p>DR. BORER (committee, <b>voted yes</b>):....[to Dr. Fisher] you are suggesting that if we do think there is a subgroup or subgroups of patients that could reasonably get this drug without additional data about efficacy with regard to an endpoint, like anti-ischemic efficacy, that at least see some data about what has happened to patients drug who fell into that subgroup. (p.147)</p> <p>DR. FISHER (committee, <b>voted no</b>): Doesn't that seem fairly minimal? (p.147)</p> <p>DR. LIPICKY (FDA): [to Dr. borer] But, indeed, you see, look, you are saying much more than that. You are saying any other beta blocker that is rapidly acting. Just show us your blood levels versus a time curve and that you are a beta blocker and you have it made. Right? (p.148)</p> <p>DR. BORER (committee, <b>voted yes</b>): For certain indications. (p.148)</p> <p>DR. LIPICKY (FDA): Oh, oh, I hear that. But the enunciation is, show me your pharmacokinetics and that you are a beta blocker, and, you know, don't even bother going to people..... (p.148)</p> <p>DR. BORER (committee, <b>voted yes</b>): Presumably, you got the pharmacokinetics in people. you raise is a good about experience in ought to be given. But, okay, I think that the point that one. We should at least have some data people to whom we are suggesting the drug I presume such experience is available and could be given to the FDA. (p.148)</p> <p>DR. KASSES (committee, <b>voted yes</b>): I guess I am a little disturbed again by the contention that there are no data..... (p.148)</p> <p>DR. BORER (committee, <b>voted yes</b>): ....perhaps we should see some information about safety and effectiveness for heart rate, blood pressure, at least in the population that we are saying might be at sufficiently high risk to warrant approval of the drug without additional information. Perhaps we don't have such information available to us yet. Perhaps the Company has it. (p.150)</p>

Committee	Year	Drug name	Comments
			<p>DR. KOWIE (committee, <b>voting unknown</b>): Jeff, is it so difficult to also ask them to come up with another endpoint study?.... I just wanted to know --understand that. I really don't. I really share I don't Lloyd's disquiet with the way that has been handled. I don't understand why we can't get efficacy data in a group of patients who are not at high risk..... We will have data that the drug is anti-ischemic, which we don't currently have. We have no data that the drug is an anti-ischemic agent..... (p.150-151)</p> <p>Dr. Lee (Sponsor): By what mechanism would you suggest that it is anti-ischemic? (p.151)</p> <p>Dr. Kowie (committee, <b>voting unknown</b>): By its beta-blocking effect. But just because it is a beta blocker -- again it gets back to the same problem, we don't approve drugs for indications because they are in a class. We approve them because it is an empiric approach – (p.151)</p> <p>Dr. Borer: That doesn't mean that we can't do it or that we shouldn't do it or that we don't do it. We haven't done it. (p.152)</p> <p>.....</p> <p>DR. BORER (committee, <b>voted yes</b>): Is there any one of the consultants who now believes that the drug shouldn't be approved? (No response) I think they are all in agreement that it should be approved. (p.156)</p> <p>Dr. Borer (committee, <b>voted yes</b>): Since we have reached somewhat of an impasse with regard to the consideration of the initial indication, we won't discuss that aspect of the use of this drug any more. (p.158)</p> <p>.....</p> <p><i>Discussions on supraventricular tachycardia</i></p> <p>DR. KOWIE (committee, <b>voting unknown</b>): I recognize that this is a ventricular response rate controller..... (p.204)</p> <p>DR. BORER (committee, <b>voted yes</b>): Do we need to have any information about those specific populations? (p.205)</p> <p>DR. KOWIE (committee, <b>voting unknown</b>): I asked that question as the first question and I think that it would not be unreasonable at some point to go through the data base to actually look at some of the clinical parameters...(p.206)</p> <p>Dr. Borer (committee, <b>voted yes</b>): Does anyone on the Committee have any additional or any difference from what Peter (Dr. Kowie) said? (p.206) (No response) Okay, so everybody is willing to agree that the risk-benefit relationship favors benefit, even given the two caveats that we have here among the questions. (p.206)</p> <p>-----</p> <p>DR. LIPICKY (FDA): Prior to approval? [additional data review] (p.216)</p> <p>DR. KOWIE (committee, <b>voting unknown</b>): During the approval process. (p.216)</p> <p>DR. LIPICKY (FDA): We don't take that long. (p.216)</p> <p>DR. BORER (committee, <b>voted yes</b>): DO you want a consensus answer about that, Ray, or is that something that – (p.216)</p> <p>DR. LIPICKY (FDA): Yes, I think it might be worth sort of a consensus answer as to whether that really is a prior to approval requirement. (p.216)</p> <p>....</p>

Committee	Year	Drug name	Comments
			<p>DR. BORER (committee, <b>voted yes</b>): SO we need to know, (a) is it necessary to have more information and, (b) if so, about crossover to what? Lloyd? (p.216)</p> <p>.....</p> <p>DR. BORER (committee, <b>voted yes</b>): Okay. So it may be that when the FDA reviews those data, which I don't think we have seen -- .... But now you have heard that that kind of a review is necessary and there are four separate cross-overs about which you should know. (p.217-218)</p> <p>DR. LIPICKY (FDA): But only from two people have I heard that. (p.218)</p> <p>DR. BORER (committee, <b>voted yes</b>): Oh, I am sorry. Does anyone disagree with what Peter (Dr. Kowey) and Lloyd (Dr. Fisher) have said about the need for these data to be obtained before approval? (No response) No. Everybody agrees with that. (p.218)</p>
Cardiovascular	1986 (9/29)	Elanpres/ Methyldopa, NDA #19499, non-NME, non- expedited	<p><b>A FDA reviewer asked the committee that, if the committee thought the drug was approvable, the approvability was with the idea of more studies necessary post-approval. No clear answers were given. Unanimously, the committee recommended non-approval. The role of PMS is unclear.</b></p> <p><b>Votes: 0 yes 8 no (informal voting)</b></p> <p><b>Approval: rejected by the FDA</b></p> <p>Dr. Borer (committee, <b>voted no</b>): ....Now, with regard to this specific agent, do you recommend approval of Elanpres, given the base of the information that we have for use in the treatment of hypertension? And if so, would you recommend any other clinical trials that would be necessary to further clarify the characteristics of this formulation? I am not sure I understand that. If we would recommend approval, what else should be done after approval? I am not sure I understand that (question). If we would recommend approval, what else should be done after approval? (p.301)</p> <p>Dr. Lipicky (FDA): Well, really the way it was worded was if you thought it was approvable, was that with the idea that more studies would be necessary post-approval in order to characterize.. (p.301)</p> <p>Dr. Borer (committee, <b>voted no</b>): Aha, which are voluntary by nature because we can't mandate that studies must be done. (p.301)</p> <p>Dr. Lipicky (FDA): Well, no, I think that people generally go along with postmarketing study recommendations. They may not be as prompt as one would like to see them. But in general there is reasonable compliance with postmarketing recommendations. (p.301)</p> <p>Dr. Messerli (committee, <b>voted no</b>): I don't think it should be approved as a once a day drug. I would consider b.i.d. approval. And as further studies I would like to see it compared with Aldomet single dose once a day. Also I would like to see some 24-hour ambulatory blood pressure monitoring to characterize the peak effect. (p.302)</p> <p>Dr. Kowie (committee, <b>voted no</b>): There is no data that we have available on the b.i.d.</p> <p>DR. BORER (committee, <b>voted no</b>): Okay. Are there any other comments? So it appears that the Committee is in unanimity that we don't have sufficient information to recommend approval of Elanpres</p>

Committee	Year	Drug name	Comments
			at this time. And several pieces of additional information, including a better characterized time course of action, and -- well, one recommendation has been that the time course of action be better characterized, that a comparison against....(p.302)
Cardiovascular	1986 (9/30)	Cardene/ Nicardipine, NDA #19488, NME, non- expedited	<p><b>The committee was concerned about the safety profile (mortality) and lack of data on different population groups. The committee recommended for additional data before approval. No role of PMS on approval.</b></p> <p><b>No voting or counting hands for approval recommendation.</b></p> <p><b>Approval: delayed. approved on 12/28/1988</b></p> <p>Dr. Borer (committee): ...Okay, now are there pharmacologic data that could make a confirmatory study less necessary? (p.169)</p> <p>.....</p> <p>DR. PACKER: Just to clarify, ... I think that in the absence of further safety data, given the experience....., this exclusion is apparent from the data which is available to us. If the exclusion be eliminated, then we need more data. (p.183)</p> <p>Dr. Borer (committee): Wait. There is a difference, I think, we have to deal with the two different aspects of the problem, because what the company would have to do deal with the problem depends on our perception of it. If there were no other issue [than cautionary tail], the company could choose to do a study or not do a study, but the drug would be approvable on the basis of the failure issue alone. If we are saying that mortality is a concern, then the company would have to do a mortality study..... (p.184)</p> <p>Dr. Kowey (committee):....I don't understand why it would be so difficult to do both studies at the same time [progression and mortality studies] ... (p.185)</p> <p>Dr. Borer (committee): Well, do you think it is mandatory that that be done? (p.185)</p> <p>Dr. Kowey (committee): Yes. I think that once this issue has been raised of safety – (p.185)</p> <p>.....</p> <p>Dr. Borer (committee): I think there are two concerns: One is progression of heart failure in people who have heart failure, which has been suggested to be a labeling issue, although I think Craig has taken the position that it is an approvability issue as well, until experience, no? (p.195)</p> <p>.....</p> <p>Dr. Borer (committee): ....is that necessary before the drug could be approved in this group of patients? (p.200)</p> <p>.....</p> <p>Dr. Borer (committee): Would that be sufficient, or do they have to do a study in order for the drug to be approvable for use in people with class three and four failure? (p.202)</p> <p>.....</p> <p>Dr. Kowey (committee): In order to write that indication, indication for use, yes (yes a mortality trial is needed). In order to not have on the labeling that this drug is not to be used in those kinds of patients,</p>



Committee	Year	Drug name	Comments
			<p>which is the alternative. The alternative is not to include that as an indication for. (p.209)</p> <p>.....</p> <p>Dr. Lipicky (FDA): In order to allow use in class three and four, the answer was yes, you need a mortality trial. (p.210)</p> <p>Dr. Pratt (committee): So I am voting for a mortality trial. (p.212)</p> <p>Dr. Borer (committee): For any approval of the drug at all? (p.212)</p> <p>Dr. Pratt (committee): No, No. Again, I am voting exactly what I said, not what you said. I am voting for a mortality trial in this group of patients. (p.212)</p> <p>.....</p> <p>Dr. Borer (committee): Okay, so it could be approved for use for those patients for class one patients, but not for class three and four without this study being done.</p> <p>Dr. Pratt (committee): that's my feeling. (p.212)</p> <p>.....</p> <p>DR. BORER (committee): So you are saying that there has to be a trial designed specifically to look at mortality in order for the drug to be approved? (p.213)</p> <p>DR. FISHER (committee): If the drug is to be approved in this population. If it's a contraindication that strikes me as a viable alternative, then it may or may not be ignored, but I would be happy with my participation to vote for approval subsequent the other data. (p.214)</p> <p>DR. BORER (committee): Okay, so the vote is that in order for the drug to be approved and there are to be no restrictions on the labeling about class three and four patients, a mortality trial of some sort has to be done. Okay. Is that the only question that you want answered? You don't want any additional information about warnings? Okay.</p>
Gastrointestinal	12/8/1986	Ethamolin/ ethanolamine, NDA #19357, NME, Priority, Orphan	<p><b>The committee faced the difficulty of obtaining controlling data for a substance that has come into common usage for unapproved indication. There was a lack of data but they were willing to approve the drug with less data. When voting, the committee favored approval by a margin of 4 to 3, but the role of PMS was not observed.</b></p> <p><b>Votes: 4 yes 3 no</b></p> <p><b>Approval: 2 years delayed. 12/22/1988</b></p> <p>Dr. Temple (FDA): It often turns out that the conditions that drug turn out to be orphan for are comparatively difficult to study or comparatively uninteresting to people to study. And whether we designate something as an orphan or not, we have tended in the past to take that into account, at least to some extent. And if you go back before there was an Orphan Drug Bill or Orphan Drug Office, drugs for relatively small numbers of people or drugs that were not anybody's baby were often looked at in much the same way they are now. For example, it would be very unusual to rely on studies entirely in the literature without the full case reports, without the randomization codes, and all the rest of it, for a typical new molecular entity. But it is unlikely that one is going to be able to find anything</p>

Committee	Year	Drug name	Comments
			<p>else and so we have tended to be more generous. I am not sure what that says. I think the standards are the same; standards of safety and effectiveness are the same. But there is a willingness to go a little further in looking at kinds of data that would probably not be sufficient for a new antihypertensive agent. And it is a matter of judgment about how far to go. (p.137)</p> <p>.....</p> <p>Dr. Ransohoff (committee, <b>abstained</b>): And the third question is, is it necessary, before approval, for issues to be resolved about exactly which patients and when in the course, and also the details of the sclerosing -- the details of the entire technique and procedure, do those need to be resolved before approval? (p.132)</p> <p>DR. TEMPLE (FDA): Well, how resolved they have to be is a matter of judgment. ... When there is uncertainty about the best way, the labeling can be silent about it, recommend one way of doing it and say so, and we have, from time to time, put into the labeling what the areas of uncertainty were. You do, I think, have to be able to identify one technique that is acceptable and one group of people that it is reasonable to treat. We often don't know everything though at the time of approval. So you don't have to have all the questions resolved. (p.140)</p> <p>Dr. Lipicky (FDA): I must admit a little bit of fuzziness in terms of what question is a relevant question to ask. ... if a sclerosant seals off a vein and esophageal varices are diseases of veins that lead to bleeding, why are we even discussing it as to whether or not it is approvable? And it seems to me the very fact that we are discussing it implies that we, as a body of people, expect some relevant clinical outcome to have occurred from having squirted the sclerosant into the vein. So in that sense, it seems to me that the expectation is not if you put a sclerosant into a vein will it sclerose, but do you know how to put the sclerosant in, how much should you put in, and if you do put it in correctly, do you get something useful from having done it? (p.140)</p> <p>.....</p> <p>Dr. Wilson (committee, <b>voted</b>): I think there are several things that the Committee can do. The Committee can recommend approval of the proposal as it has been presented. The Committee can recommend disapproval of the proposal. The Committee can do anything else in between. It can recommend contingent approval with respect to additional information, with respect to so forth and so on. (p.185)</p> <p>DR. BUTT (committee, <b>voted no—voted for contingent approval</b>): I would recommend contingent approval, contingent on more information concerning the same points made by Dr. Schapiro, that comparative studies be carried out with the agents present time. (p.186)</p> <p>Dr. Szabo (committee, <b>voted yes</b>): ....every drug has to be introduced first and in this case the sponsor and the Agency happened to pick up this drug first to make the data base as it is available. And it might be by default the drug of comparison but this is</p>

Committee	Year	Drug name	Comments
			<p>the first drug which has been packaged for potential approval. So I would recommend approval. (p.187)</p> <p>DR. FLESHLER (committee, <b>voted yes</b>): .. I would feel a lot more comfortable if we did something that we have never done here before, at least in my term of office, and that is to defer the decision because I really feel that from the sort of basic data that we were all arguing about, I think there probably is more to be gotten out of it than we have gotten and I think we could challenge the FDA and ourselves to look at the various articles and try to get behind them as best we can to see if we can make ourselves happier about those data bases and, you know, use that as a firm thing. I think the business of wanting comparisons with other agents is unrealistic....Is this drug better than doing nothing is what our job is and, you know, I think the weight of opinion is better than doing nothing, in which case, if you force me to make a decision, I vote with Sandor and vote for approval. But I would request at least the opportunity to re-examine the data and have the data re-examined by the FDA experts. (p.188)</p> <p>DR. THISTLE (committee, <b>voted yes</b>): Well, having heard this data hashed through many times over the past six or eight years, I am not optimistic that the water is going to be any clearer after they are studied further. I side in favor of having some control over an agent and some control over labeling and its use, rather of approval. (p.188)</p>
Cardiovascular	5/29/1987	Streptokinase/ Streptase/ Kabikinase, BLA (number not available), non-NME, non-expedited	<p><b>The committee unanimously favored approval on the basis of mortality results from two major studies. The long-term mortality was on-going and the committee and FDA discussed about postmarketing studies. The role of PMS on approval is unclear. Votes: no votes, but unanimous opinion on approval Approval: 11/5/1987</b></p> <p>Dr. Pratt (committee): I don't think that the long-term mortality data is as strong, only because it is preliminary information. It is certainly compelling, and it is promising and needs to be further identified in terms of the data being peer reviewed and being left open to all the reviews that are appropriate (p. 328)</p> <p>.....</p> <p>Dr. Borer (committee): In addition, perhaps it might be worth suggesting that we might feel, and we might believe that it would be beneficial if the company, the sponsors, would choose to firm up data with regard to some of these other .... (p.332)</p> <p>.....</p> <p>Dr. Zuck (FDA): ..myocardial function studies, I know there is no claim for myocardial function studies, but are the data that were presented sufficient that we could license without additional myocardial function studies or is it the wish of the Committee that they be gotten in Phase IV or what precisely was the conclusion? (p.369)</p> <p>Dr. Borer (committee): The conclusion was that we didn't have sufficient data...</p> <p>Dr. Zuck (FDA): you don't believe there is sufficient data to recommend approving that claim....but you could approve the claim for mortality?</p> <p>Dr. Borer: yes.</p>

Committee	Year	Drug name	Comments
			Dr. Zuck (FDA): are you absolutely sure that if the long-term follow-up data was as presented here with Dr. Pratt's proviso, then Dr. Pratt's conclusion is the total conclusion of the committee? .... There is a reason I am asking.... the Yusuf data and the GISSI data when it is all in front of us and the ISAM data all suggest that what we heard today was as it is, then no additional long-term study data would be required in your opinion to be approvable. (p.370)
Cardiovascular	5/29/1987	Activase/ Alteplase, BLA #103172, NME, non- expedited	<p><b>The committee acknowledged TPA's efficacy at dissolving clots in coronary arteries, but decided not to recommend approval with safety concerns and not well-established dosage. From the committee transcripts, no clear evidence that PMS played any role in approval was observed. The FDA unusually speeded up approval with postmarketing studies. However, the role of PMS on approval is unclear.</b></p> <p><b>Votes: 1 yes 6 no</b>  <b>Approval: 11/13/1987</b>  <b>FDA Commissioner Young announced approval of Genentech's Activase (alteplase) on Nov. 13. "FDA did move exceptionally rapidly, proactively, in this process. Usually, after a negative advisory committee recommendation, it takes at the minimum of one year, to seven years on the outside, to have that particular recommendation answered and revised by other studies." The agency's objective in the re-review of the TPA application was to answer the questions raised by the advisory committee. FDA convened a Sept. 2 meeting of the consultant panel. At that first meeting, the ad hoc group also rejected approval, deciding that the supplemental data were not sufficient. Genentech has agreed to undertake further Phase IV studies on TPA. Young said the agency is "looking forward ... negotiating and working with [the company] in designing the appropriate studies so that they will go on and we'll see some comparison studies."</b><sup>230</sup></p> <p>Dr. Alving (not a committee--identity unclear): ....I believe there were arrangements to do a postmarketing surveillance, and this is so that you can see when the drug is unleashed on the community at large how it is accepted.... People would think, well you just lyse coronary clots and no other clots and maybe have a false sense of security, but a post-marketing surveillance could do that, and I think you would really want to check the advertising, too. (p.539)</p> <p>Dr. Borer (committee, Chair, <b>didn't vote</b>): We do have the option of going step further and requesting a postmarketing study rather than postmarketing surveillance ...and we have done it several times with regard to similar problems in other drugs. (p.539)</p> <p>.....</p> <p>Dr. Fisher (committee, <b>abstained</b>): If the drug were licensed and then ongoing trials against placebo came in say, with an estimated zero</p>

<sup>230</sup> <https://pink.pharmaintelligence.informa.com/PS012762/FDA-BREAKS-TPA-APPROVAL-BLOCK-AD-HOC-ADVISORY-GROUP-CALLED-IN-TO-SUPPLEMENT-ADVISORY-COMMITTEE-AND-I> [The pink sheet, 16 Nov 1987]

Committee	Year	Drug name	Comments
			<p>effect...., do you have the mechanisms to then withdraw the approval? (p.526)</p> <p>.....</p> <p>Dr. Fisher (committee, <b>abstained</b>): In that case, I guess I will abstain because if when these other things come in and there was no effect, it would be withdrawn, then I am in favor of it because I am sort of the lay person representative here. I am not an MD. ...but to the extent I understand...I think there is a lot of evidence, and the animal evidence was alluded to indicate that lysing clots is to a fairly high degree of certainty very probably the mechanism of what is going on with streptokinase, but if this other data came in the other way, then I would have to say "Gee, you are wrong again" so that makes a lot of difference. If once the genie is out of the bag there is no way to undo, even in the face of the other evidence, or it is very likely it would be undone, I would vote no. If that is sure to be done, I will vote yes. And since we don't know, I will abstain." (p.527-528)</p> <p>.....</p> <p>Dr. Packer (committee, <b>voted yes</b>): ...enough pieces have fit together to consider it, consider clot lysis for this particular agent as an endpoint that it could be labeled for. (p.544)</p> <p>Dr. Lowenthal (committee, <b>voted no</b>): I agree that there is very good evidence that rt-PA does lyseclots. I think that I would like to see more data in terms of -ventricular function, and the other discussions that we had still pertain. So, I would withhold my approval until more data is at hand. (p. 544)</p>
Cardiovascular	12/7/1987	Primacor/ milrinone, NDA #19436, NME, non- expedited	<p><b>There was a discussion about whether it is okay to approve without more study. There was consensus that PMS would be appropriate. No role of PMS.</b></p> <p><b>Votes: 5 yes 3 no</b></p> <p><b>Approval: 12/31/1987</b></p> <p>DR. HARRELL (committee, <b>voted no</b>): I guess the question becomes are we ready to let the drug loose? Do we need more follow-up to be able to tell with confidence that this mortality is not really worse? (p.228)</p> <p>DR. TANDON (sponsor side): Dr. Harrell, I would like to remind you that we have had six-months of follow-up data from the multi international trial here, and we did not see any adverse affect of milrinone on survival. (p.228)</p> <p>DR. SCHWARZ (sponsor side): Dr. Harrell, if I may point out, although it's open-label the follow-up in the open-label trial for up to four years after adjustment for ejection fraction differences is exactly consistent with that seen at three months. So we extend it out to six months in a controlled trial and out to four years in an open-label trial. (p.228)</p> <p>.....</p> <p>Dr. Pratt (committee, <b>voted no</b>): I understand from the sponsor that were this to be approved, the intravenous formulation, that some Stage 4 studies in post infarc patients, post-surgical patients, would be things that would be thought about. (p.305-306)</p>

Committee	Year	Drug name	Comments
			<p>Dr. Packer (committee, <b>voted yes</b>): I do not know that, but I would not restrict the use of the drug because I did not know that....I think that it would be very easy to address the efficacy of milrinone at 48 hours in a very, very rapid fashion. Would I hold up approval of the drug because of that, the answer is no. (p.307)</p> <p>.....</p> <p>Dr. Morganroth (Advisor): From a safety point of view, we were not convinced that there was evidence that milrinone increased mortality regarding survival issues, and that is with data in close to the 1500 patients, we obviously would like to see more data in some Phase 4 experience to be more comfortable with that statement -- would be appropriate, but as the data sits, we are not too uncomfortable with the issues of survival, nor are we too uncomfortable with the issue of proarrhythmia. (p.310-311)</p> <p>.....</p> <p>DR. LOWENTHAL (committee, <b>voted yes</b>): I think that if we get into Phase 4, there could be some additional studies done to corroborate 706 and 712. But, as it is right now, I think there is sufficient evidence to speak in favor of the inotropic activity of milrinone and forget the issue of dig right now, because we are going to be here until tomorrow trying to debate that issue and we really don't have an answer. (p.355)</p>
Cardiovascular	11/3/1988	Lopressor/ metoprolol tartrate, NDA #17963, Supplemental	<p><b>Metoprolol was originally approved for hypertension, angina, and acute myocardial infarction on 08/07/1978. The sponsor suggested an indication for cardiac arrhythmias. During the course of the discussion, the committee raised several questions. The committee and FDA agreed that the NDA needs further analysis, and possibly additional studies, before a decision on approvability of the drug can be made. The sponsor directly asked whether postmarketing studies could serve the purpose, but the committee unanimously decided to not recommend approval. No role of PMS.</b></p> <p><b>Votes on treatment for premature ventricular contractions (PVC) without symptoms: all voted no. Votes on treatment for symptomatic PVCs without symptom data: all voted no.</b></p> <p><b>Approval: Lopressor was not approved for arrhythmias. It is unclear whether there was an official postmarketing study for this NDA at the time of approval.</b></p> <p>Dr. Henis (sponsor, Ciba-Geigy): symptomatic PVC3 -- and we are not, to be clear, seeking a claim for non-symptomatic PVCs -- are a common clinical problem. People come to their doctors and say, "I'm having palpitations" and, Milton, despite your statement, I do not think that only 0.002 percent of people who are having significant numbers of PVCs are symptomatic. Some real proportion of people are bothered by them. Okay?</p> <p>Now, if you are going to say that we are not going to approve beta blockers, the safest class of antiarrhythmic agents, with data that has shown, at least in one population, decrease in mortality in a sick population....the result will be that people will use much more</p>

Committee	Year	Drug name	Comments
			<p>dangerous agents to treat simple symptomatic PVCs. By doing so, they will, in fact, wind up causing harm.</p> <p>I would suggest also that there may be another possibility, at least as far as metoprolol is concerned, and that is that I am sure the Company would be willing to do a Phase IV study to show that....It just seems to me that there is some dancing on the head of a pin here. We are not suggesting that this drug be used for asymptomatic PVCs. We are not suggesting it be used for prevention of sudden death or that it be labeled the same. We are suggesting it be approved for symptomatic PVCs. I think that somehow you have gotten way off track. But I would ask you to consider the possibility of such a Phase IV study if that really concerns you. (p.33, second part of the transcript)</p> <p>....</p> <p>Dr. Temple (FDA): Marc (Dr. Henis) is talking about what their claim is and the claim is not exactly what they studied. That's the problem. (p.34)</p> <p>Dr. Henis (sponsor): .... It is reasonable to consider PCVs as a surrogate endpoint because many people with large numbers of PVCs are symptomatic with palpitations and that bothers them a lot and it interferes with their functioning. Beta blockers help them a lot by lowering the numbers of PVCs and by improving their symptoms. Symptoms do not have to be life-threatening in order for their removal to benefit a patient.</p> <p>Dr. Packer (committee, <b>voted no</b>): Marc, all I would say is that if they are so common, all you have to do is go out, find them, study them in a placebo-controlled trial and show it works.</p> <p>Dr. Henis (sponsor): Would you be willing to consider that as a Phase IV commitment?</p> <p>Dr. Packer (committee, <b>voted no</b>): My suggestion would be that it is difficult to approve a drug before you prove it works so you can prove it works after it is labeled.</p> <p>Dr. Henis (sponsor): we have proved that it lowers PVCs. What you are unwilling to conceive is that simple PVCs can be symptomatic....</p> <p>Dr. Lipicky (FDA): what Milt is not willing to accept I think is that if you make PVCs go away you make the symptoms go away.</p> <p>Dr. Henis (sponsor): Well, I would suggest that that is an unreasonable position.....</p> <p>Dr. Morganroth (sponsor): I'm just very curious as to why the people on this committee are unwilling to accept what seems to me an absolute certainty, that if you assume that PVCs can cause symptoms,....if you get rid of the PVCs, that is sufficient to assume that if you treat patients who have symptoms from them, by definition, the symptoms must disappear.</p> <p>....</p> <p>Dr. Pratt (committee, <b>voted no</b>): ...because we do not have the answer. You know you do not have the answer either. We have patients in whom we suppress arrhythmia and they still have symptoms. .... Intuitively I totally agree with you..... But the individual patient correlation is not so good and nobody has really produced a data base to say that it is good.</p>

Committee	Year	Drug name	Comments
			Dr. Morganroth (sponsor): If you really believe what you say, that it is so difficult and so hard to believe you can actually make this correlation, then to make that a requirement, which is what I hear the committee suggesting, for not only beta blockers but all antiarrhythmic drugs would markedly inhibit their potential approvability.....
Antimicrobial	5/1/1989	Nebupent/ Aerosolized Pentamidine, NDA #19887, non-NME, Priority, Orphan	<p><b>At least one of the committee argued for conditional approval on phase IV studies. Because there was no regulatory tool to require postmarketing studies, the member strongly wants the FDA to recommend phase IV trial. Many presentations were given by sponsors, FDA, and public including ACT/UP, an AIDS advocacy group before the committee discussions. No role of PMS.</b></p> <p><b>Votes: 9 yes 0 no</b> <b>Approval: 6/15/1989</b></p> <p>DR. KUNIN (committee, <b>voted yes</b>): I want to reiterate that there has to be a large-scale trial on primary prophylaxis in....That is essential and I should think that is a condition of approval for primary prophylaxis that there be a Phase IV study done. So I would like to emphasize that further by saying that it is conditional. (p.262)</p> <p>COMMISSIONER YOUNG (FDA): A point of information and a order, the Food and Drug Administration does not have the authority to require a Phase IV study. It is not legally possible to give a conditional approval. However, I have never seen a study that was not strongly urged by the Food and Drug Administration that was not followed in a Phase IV study. But I did want to make that point of order. (p.263)</p> <p>DR. KUNIN (committee, <b>voted yes</b>): May I respond to that? I accept that point of order and I will withdraw that conditional and strongly advise. (p.263)</p> <p>DR. COOPER (committee, <b>voted yes</b>): ....I think everybody would agree that long-term safety information is necessary. (p.264)</p> <p>DR. KUNIN (committee, <b>voted yes</b>): The bottom line is that we cannot withhold approval, in my opinion, of primary prophylaxis but we also have to have that nagging concern that the direct evidence is not there, and therefore, urge as best we can that studies be done, whether they are sponsored by the NIH or we watch what is happening so that we know that we are accomplishing something in the long run. (p.265)</p>
Cardiovascular	2012 (9/13)	Phenylephrine hydrochloride, NDA #203826, non-NME, non-expedited	<p><b>The committee expressed concerns for approval for a broad indication. Those who voted yes noted that trust must be put in physicians who have used this drug for years. Some role of PMS was recognized by a member (Dr. Sager) who voted no but said that a very narrow indication with PMS would make sense.</b></p> <p><b>Votes: 2 yes 8 no</b> <b>Approval: approved on 12/20/2012</b> <b>PMS: 1 PMR—pediatric study</b></p> <p><i>PMR #1 (PREA): Conduct a trial in the ≥12 - 16 year old age group to evaluate the dose effect of phenylephrine hydrochloride injection on</i></p>



Committee	Year	Drug name	Comments
			<p><i>blood pressure in patients undergoing general anesthesia and neuroaxial anesthesia.....</i></p> <p>Dr. Targum (FDA): If we were to rely on publications as the sole basis of our safety assessment, number one, it's not clear how actively the safety data were even collected. And has already been mentioned, there's variable mention of adverse events in the publications. However, there is a long history of experience here, and we have the additional tool of post-marketing surveillance. (p.72)</p> <p>.....</p> <p>Dr. Lincoff (committee, <b>voted no</b>): Safety data in the application were obtained from publication and post-marketing reports. There is no overall analysis of exposure. How confident are you that the safety profile has been adequately characterized in the submission, and is there additional safety information that the agency should request? If so, should this information be requested pre-approval or post-approval? (p.155)</p> <p>Dr. Lincoff (committee, <b>voted no</b>): But for an approval for perioperative anesthesia, does anyone believe that there's additional information that should be required pre-approval? And does anyone believe that as a contingency of approval, there should be a post-approval requirement for additional information for that indication? (p.158)</p> <p>.....</p> <p>Dr. Tobin (committee, <b>voted yes</b>): So I would suggest that we have no hesitancy about helping the sponsor if you think you have enough efficacy data already. There's decades of safety at this point, but I'm not at all hesitant about more post-marketing surveillance data for safety. (p.164)</p> <p>Dr. Lincoff (committee, <b>voted no</b>): But if an indication is sought for anything other than neuraxial, I believe that pre-approval as safety information in those other settings should be. That doesn't mean that it can't be used, but if the mark of an indication is desired, the legitimacy of an indication, then there should be data. (p.165)</p> <p>.....</p> <p>Dr. Sager (committee, <b>voted no</b>): I voted no.....I am sympathetic, however, to the situation of patients undergoing general anesthesia who may have a specific need for the agent, and I would think that maybe a very narrowly worded indication with a post-marketing, either some type of either study or some other type of post-marketing data collection looking at safety in that population would make sense. (p.171)</p> <p>.....</p> <p>MR. MCGLAMERY (committee, <b>voted yes</b>): I just think that gathering that type of information for pre-approval in these cases, I think it would have been better to try to get some data that maybe had already been collected but hasn't been collated properly and then add some new data to that on top of it post-approval instead of voting against it. (p.175)</p>
Gastrointestinal	2012 (8/28)	Humira/ Adalimuma	<b>Humira was originally approved for rheumatoid arthritis in 2002. Abbott applied for a new indication for ulcerative colitis. Thirteen</b>

Committee	Year	Drug name	Comments
		b, BLA #125057-232, Supplemental, Non-expedited, orphan	<p><b>out of 16 voting members (1 abstained) indicated that there is no additional study that should be conducted prior to approving Humira. Fifteen out of 17 voting members indicated favorable BR profile. One committee member (Dr. Fleming) recognized some role of PMS on approval. The majority agreed that the drug needs PMS but not necessary for approval. Recognized role of PMS.</b></p> <p><b>Votes: 15 yes, 2 no on favorable B-R ratio</b></p> <p><b>Approval: approved on 9/28/2012</b></p> <p><b>PMS: 6 PMRs and 1 PMC</b></p> <p><i>PMR #1: A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).</i></p> <p><i>PMR #2: A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal.....</i></p> <p><i>PMR #3: Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference.....</i></p> <p><i>PMR #4: Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.</i></p> <p><i>PMR #5: Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg.....</i></p> <p><i>PMR #6: A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission.....</i></p> <p><i>PMC #7: Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis.....</i></p> <p>Dr. Zhu (committee, <b>voted yes</b>): So, in that regard, for the TNF pre-treatment group, you could -- it may require dosing change. But I agree it should go to a post-approval study. (p.236)</p> <p>.....</p> <p>Dr. Rood (committee, <b>voted yes</b>): Do we have any mandate – and that's probably a bad word. But what will happen should this drug get approved for this indication at this time? What happens</p>

Committee	Year	Drug name	Comments
			<p>postmarketing? Do we have that concern at all, or should we be concerned of that at all? (p.257)</p> <p>.....</p> <p>Dr. Fleming (committee, <b>voted no</b>): I thought the first part of your question, though, also involved, is there any role for this committee to think about what a postmarketing study might be if we felt that that could be influential in deciding whether to approve. And my understanding is yes, and that's part of what's going on in question number 5. My understanding is if you generally were concerned, but thought that your best sense of the data was favorable benefit to risk, but you really had uncertainties about issues such as, is this the optimal dose, or we need to know more about safety, you could approve and then you could recommend that those studies be done as a way to alleviate some of the concerns you would have with approval if you were on the fence, so to speak. (p.259-260)</p> <p>.....</p> <p>Dr. Kumar (committee, <b>voted yes</b>): Moving on to the third question, which is also -- third item, which is also a voting item. Are there additional efficacy studies that should be conducted prior to approving Humira for moderately to severely active ulcerative colitis? (p.296)</p> <p>Dr. Rice (committee, <b>voted yes</b>): Michael Rice. I voted no [to pre-approval studies]. I did not feel that further studies are needed, which I think would delay a very potentially important medication for our patients, although I do think further studies are needed, but not necessarily for the approval of this agent. (p.297)</p> <p>Dr. Losavio (committee, <b>voted yes</b>): I voted no [to pre-approval studies] as well. I don't think that the approval of the medication should be held up. (p.298)</p> <p>Dr. Kumar (committee, <b>voted yes</b>): I voted yes -- I'm sorry. I voted no [to pre-approval studies]. Not necessary before the drug is approved, clearly more trials are needed. I think we need to have post-approval follow-up. But data to this point are favorable. (p.300)</p> <p>.....</p> <p>Dr. Barrett (committee, <b>voted yes</b>): Jeff Barrett. I voted yes, again with the presumption that the benefit will be actually better when some of these additional studies trying to understand the optimal dose are conducted, and in particular, understanding with more granularity who's likely to respond. I think you can limit the nonresponder population so that in a smaller subset of patients, the benefit/risk will be better. (p.308)</p>
Gastrointestinal	10/16/2012	Gattex Kit, Teduglutide Recombinant, NDA #203441, NME, non-expedited, orphan	<p><b>The committee had a consensus that the drug is effective and its benefit outweighs risk despite the potential tumor promoting effects. Some members were particularly concerned about the enforcement of the postmarketing studies. There was a voting question on REMS: 10 members voted yes, 1 member voted no, and 1 member abstained. All voted for favorable BR. No clear evidence of the role of PMS on approval.</b></p> <p><b>Votes on benefit-risk: 12 yes, 0 no</b></p> <p><b>Approval: approved on 12/21/2012</b></p> <p><b>PMS: 1 PMR</b></p>

Committee	Year	Drug name	Comments
			<p><i>1 PMR: A prospective, multi-center, long-term, observational, registry study, of short bowel syndrome patients treated with teduglutide in a routine clinical setting, to assess the long-term safety of teduglutide. .... Patients should be enrolled over an initial 5-year period and then followed for a period of at least 10 years from the time of enrollment. Progress updates of registry patient accrual and a demographic summary should be provided annually. Registry safety data should be provided in periodic safety reports.</i></p> <p><i>Discussions on postmarketing surveillance</i></p> <p>Dr. Grand (committee, <b>voted yes</b>): So personally I would feel that this is an adequate endpoint, and I agree with both of you, that a more robust data analysis scheme would have been helpful to us, but in the long run I don't think it's going to significantly influence our decision today, but I do think it might encourage us to encourage the FDA to have a really robust post-marketing surveillance program for the company to participate in, and I like the idea that they were going to do a registry.....I hate to say malignant potential, but I guess that's there, that this agent has. (p.222)</p> <p>Dr. Sood (committee, <b>voted yes</b>): I think there is not enough evidence for the small bowel tumors, though there is some concern. So I don't think in absence of a very good kind of a screening modality in different subsets of patients, it may be really imperative to kind of recommend some kind of a surveillance, but I think we learn in the post-approval surveillance period more from the registry data, and probably the concern is over the long time, and I believe this drug will be for an indefinite period, and when we go beyond 5 and 7 years, what will happen? So I think at this time I'm okay with the recommendations and the opinion of other panel members. (p.233)</p> <p>.....</p> <p>Dr. Earle (committee, <b>voted yes</b>): Regarding the registry, what is the difference between if the registry is part of REMS or if the registry is a recommended post-marketing study? Is there more enforcement that it actually happens or anything like that? (p.257)</p> <p>Dr. Korvick (FDA): If we decide that it's an important post-marketing required study, there are actions under FDAAA that are made to ensure that the study gets done, gets carried out. There are monetary penalties the sponsor has to pay if things aren't working out well. So as a post-marketing required safety study, if that was so recommended, there are elements that we can use in the law, the FDA Amendments Act, to enforce that getting done. (p.257)</p> <p>.....</p> <p>Dr. Morrato (committee, <b>voted yes</b>): I heard some conflicting information as to what's the patient norm for treatment.....So if we had some better data to better describe the care environment, I could have voted yes [to the adequacy of REMS plan] as well, but I think it's important that the patient also understand this and that there is some evaluation. So if that's a post-marketing study, not a REMS study, that's up to you, but that's why I voted no, and I just wanted to raise the point. (p.264) (here the vote was on REMS)</p> <p>....</p>

Committee	Year	Drug name	Comments
			DR. ALBRECHT (Industry rep, no voting right): I think the registry, as proposed, would be adequate if it is a mandatory registry, in other words, we make sure that it is kept and that the data are entered. (p. 280)
Antimicrobial	11/2/2012	Raxibacumab, BLA #125349, NME, Fast track, Priority, Orphan	<p><b>This BLA is for the treatment and prophylaxis of inhaled anthrax and this approval was based on animal efficacy study due to infeasibility of clinical studies. Concerns expressed by the committee in 2009 have been answered by the follow-up data sufficiently, the committee says. The committee unanimously voted yes to a favorable BR profile. A committee member said that PMS will be helpful and another member said that PMS is very important and wish that there was a protocol. But, those wordings were unclear and this case presented good safety and efficacy. Unclear evidence for the role of PMS on approval.</b></p> <p><b>Votes: 18 yes 0 no on BR profile</b></p> <p><b>Approval: approved on 12/14/2012 (with animal efficacy data)</b></p> <p><b>PMS: 1 PMR and 1 PMC—see below, 2 other PMCs are sensitivity/contamination assay and spiking studies.</b></p> <p><i>PMR #1 Conduct a field study to evaluate the efficacy, pharmacokinetics, and safety of raxibacumab use for Bacillus anthracis in the United States.</i></p> <p><i>PMC #2 Conduct a Phase 4 study to evaluate the effect of raxibacumab on immunogenicity of anthrax vaccine.</i></p> <p>Dr. Farley (FDA): So, one of the things that we benefit from the Advisory Committee -- and you could see Dr. Cox and I writing rather furiously -- is if the Committee should recommend approval, and if the Agency should approve this product, we certainly have options to be discussing, for example, post-marketing commitments with the sponsor, and that's certainly something that could be on the table, so we really appreciate your thoughts on that. (p.182)</p> <p>.....</p> <p>DR. VIETRI (committee): I voted yes. Again, I don't have any problems, at least I don't see any problems with the safety. And, of course, the post-marketing surveillance will be helpful as well. But I have no problem. (p. 240)</p> <p>Dr. Carpenter (committee, voted yes): I voted yes as well. I was reassured with the follow-up studies from the concerns from 2009 regarding the CNS effects and concerns with the antibodies. So I'm comfortable with that. (p.241)</p> <p>.....</p> <p>Dr. Katona (committee): I voted yes. I'm certainly satisfied with the necropsy studies, the 400 or so patients that were actually administered the drug. And the fact that this might spur more antitoxin research I think would be good. I mentioned previously that the post-marketing commitments are very important. I would have liked to see those protocols before we actually convened here because it's a lot of unknowns. (p.243)</p>
Oncologic	2014 (11/6)	Triferic, NDA	<b>The committee felt that the study design was complex and bit artificial. A member suggested that a Phase 4 be conducted if approved. The committee agreed that FDA needs to require</b>

Committee	Year	Drug name	Comments
		#206317, non-NME, non-expedited	<p><b>postmarketing studies if approved. No evidence of the role of PMS on approval, however, was observed.</b></p> <p><b>Votes: 8 yes 3 no</b></p> <p><b>Approval: Approved on 1/23/2015</b></p> <p><b>PMS: 2 PMRs but these are pediatric studies.</b></p> <p><i>PMR 2853-1 Complete the trial and submit the final report for the pediatric pharmacokinetic trial entitled "Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis.</i></p> <p><i>PMR 2853-2 Efficacy and safety trial of Triferic via hemodialysate in pediatric patients aged less than 18 years with hemodialysis-dependent chronic kidney disease.</i></p> <p>Dr. Zones (committee, <b>voted yes</b>): I voted yes. I didn't feel like this was a real solid yes. I was concerned about methodological problems. And I thought the sponsor did a good job laying out the protocol, but it was so complex it I think made it quite difficult. Anyway, I would suggest that if the FDA does approve this product, that there be a phase 4 study or a post-approval follow-up. (p. 188)</p> <p>.....</p> <p>DR. FOJO (committee, <b>voted no</b>): I voted no. In the end, I thought that the study wasn't all that well designed, and that made it difficult for us to come to a good conclusion.....So I just wasn't happy with it. I know you tried to get the FDA to pony up as to whether this was long-term. I think that that's an important issue that you're concerned about, to say, "Oh, this is fine," but 696 patients have 780 years of exposure. The average patient is one year. And for something that we'll do indefinitely just did not feel comfortable to me. (p.189)</p> <p>.....</p> <p>Dr. Cole (committee, <b>voted no</b>): I voted no. It was not a strong no. I felt that the data show clearly that Triferic is active versus placebo. But when I only viewed in the sense where you're going to see the biggest difference between the two arms -- so I viewed the totality of the information as being we have proof of principal but not in terms of clinical practice. I would have liked to see a study that assessed it, the more realistic clinical setting. (p. 190)</p> <p>DR. ARMSTRONG (committee, <b>voted yes</b>): I'm Deb Armstrong, and I voted yes.....My concern is that the actual use of the drug will be quite different than from the day it is presented. On the other hand, I'm actually trying to imagine a well-controlled, randomized, phase 2 trial, where you mandate what's going on when the things you're going to mandate are not things that are FDA approved. And it sounds like both the nephrologists on the panel here as well as from the sponsors sort of grit their teeth and do things that they don't really like doing such as giving more IV iron. I'm not even sure what the right trial design would be, but it seems to me that the very prolonged use of this agent, that there needs to be some safety and potential efficacy studies looking at much more prolonged use of the agent. (p.190-191)</p> <p>....</p>

Committee	Year	Drug name	Comments
			<p>DR. ARMSTRONG: So just to summarize for question 2, I think we are in agreement that there needs to be another study done to document efficacy in terms of reducing ESA requirement or assessing impact on ESA requirement, and we've heard a few things. (p.201)</p> <p>DR. ARMSTRONG: I'm also -- just because of the variation in the ESA use, if you looked at this study at the halfway point, you actually would have gotten exactly -- the opposite response. With regard to question 1, I think, as you've heard from most of us, we would certainly think it was worthwhile to do a well designed trial to try and look at whatever is the standard of care, whether it's got FDA approval or not, compare to this and see if there's an improved outcome. (p.201)</p>
Oncologic	7/9/2015	Portrazza, BLA #125547, non-NME, Fast track, Orphan	<p><b>The majority agreed that this drug has favorable BR profile. A member said that having confirmatory information before making a final decision is worthwhile. Some other members felt that they should make a decision based on the currently available data—not considering postmarketing that would make them feel good now. A consumer rep, temporary voting member of the committee, said that she feels comfortable with moving forward if good monitoring is assured. Mixed views on the role of PMS.</b></p> <p><b>No voting—discussion only.</b></p> <p><b>Approval: approved on 11/24/2015</b></p> <p><b>PMS: no PMR/PMCs reportable under 506B –non-reportable studies are usually Chemistry, Manufacturing, and Controls (CMC) related, stability related, and not required for approval.</b></p> <p>Dr. Liebmann (committee): .... But overall, I think that this was a well conducted large study. I'd love to see a confirmatory trial. I think that the toxicities were what I would expect and were acceptable in both the INSPIRE and SQUIRE trials. So I think that if we're going to play on a level playing field of what's been approved in non-small cell lung cancer to date, this is sort of in there. (p.139)</p> <p>.....</p> <p>DR. PAZDUR (FDA): And Deb, that was one of the points that we wanted to have the sponsor do --.... -- a safety study if we were going to move toward an approval. (p.150)</p> <p>.....</p> <p>DR. MENEFE (committee): .....I think when we have additional studies that would potentially be confirmatory in terms of response as well as safety -- or efficacy as well as safety, I think looking at the data before making a definitive decision, based on one phase 3 study, a well designed study albeit, may be worthwhile. (p.156)</p> <p>.....</p> <p>Dr. Pazdur (FDA): But I really want to make -- and we do not do this in the agency, nor should the committee do this, make inferences on what possibilities might be coming down the line here. We don't know what clinical trials results are before we get them, and they have to be interpreted as available therapy and approved by the FDA. (p.159)</p> <p>.....</p>

Committee	Year	Drug name	Comments
			<p>Dr. Pazdur (FDA): As I stated before, as people would use this drug, they go off, they may not be seen, their magnesium levels may be falling, and here again, we want to do everything we possibly could to address this issue rather than just noting it and not doing anything about it. (p.163)</p> <p>.....</p> <p>Dr. Roth (committee): I think we have to make the risk/benefit assessment on what we have here, not based on putative risk management strategies that may make us feel good, but may or may not save the lives of any patients down the road.....So I think we need to make the risk/benefit judgment on what we have available here today, not what might happen in postmarketing discussions. (p. 176)</p> <p>Dr. Fojo (committee): I agree with everything Dr. Roth said, and at the end of the day, this trial doesn't provide me the comfort of saying that the risk/benefit is a favorable one. It sure would be nice to have better data and additional data. So in the end, I'm convinced. That doesn't mean that there might not be some. But I also recognize this as a very, very difficult disease, and everybody's trying to do the best possible. I'm aware of that, but I just wish the data were much better than it is. (p.177)</p> <p>Ms. Mason (consumer rep, temporary voting member):....While there is just, in some respects, a very modest benefit, it is a population that needs options. And if I could be assured that people are going to have those good monitoring and good discussions about the risks/benefits for patients, I can feel comfortable with this moving forward. (p.178)</p> <p>Dr. Logan (committee): .....As we discussed, I agree that we should look at the data in its current form and not consider how can we mitigate the risks because that may or may not work. But overall survival allows us to do that. It allows us to weigh the benefit and risk very clearly, and I think patients may be willing to risk some of these toxicities for a survival benefit. (p.179)</p>
Antimicrobial	11/4/2016	Solithromycin, NDA #209006, 209007, NME, Priority	<p><b>The majority of the committee indicated that the risk of hepatotoxicity had not been adequately characterized with solithromycin, primarily due to the small size of the safety database. The vote for weighing benefit and risk was a split. One member stated that the sponsor's more detailed plan to PM surveillance could have swayed his vote. The other member stated that PM is better today and we should encourage the company to move forward. Recognized some role of PMS on approval.</b></p> <p><b>Votes on weighing benefit over risk: 7 yes, 6 no</b></p> <p><b>Approval: rejected by FDA</b></p> <p>DR. VACALIS (applicant presenter, MD): I also think Cempra's post-approval plan to monitor for potential rare safety events is important and comforting.</p> <p>.....</p>



Committee	Year	Drug name	Comments
			<p>Dr. Robles (open public hearing speaker, MD): ...some form of postmarket surveillance should provide clinicians with additional pertinent information. (p.234)</p> <p>.....</p> <p>Dr. Green (committee, <b>voted no</b>): ...So you're wanting us to give approval with the plan that you'll do this very tight vigilance afterwards and we're getting a sense that maybe we need to study more patients to demonstrate risk. (p.264)</p> <p>.....</p> <p>DR. LO RE (committee, <b>voted no</b>): ....So given all the concerns that we've had that we potentially don't have a large enough sample size of patients to adequately assess the liver signal, I'm just a little surprised that there isn't a more formal plan to, in the pharmacovigilance study, actually formally have a timing of the measurement. Has that at all been considered at all with regards to -- you're just going to wait until symptoms? That seems somewhat, I don't know, cavalier. (p.288)</p> <p>Dr. Oldach (sponsor): In the phase 4 or post-approval study that I described, we will actually write that protocol. And it will include liver function testing. In the phase 4 study..., we will write into that protocol ALT collection since we'll be collaborating with clinical science in that work. (p.288-289)</p> <p>.....</p> <p>Dr. Green (committee, <b>voted no</b>): ...I voted no... So I think we need larger numbers and perhaps creative study designs to really answer the question because my concern is that if we approve a drug, and then it ends up having to be withdrawn again, people's confidence -- the confidence of those of us who prescribe medicines, the confidence of the patients that we take care of, the confidence in the FDA, the confidence in -- and actually the confidence in the sponsors -- will all go away. So rather than making a mistake on small numbers, I think we need more data. (p.325)</p> <p>.....</p> <p>Dr. Weina (committee, <b>voted yes</b>): I voted yes. I had a hard time with it until I started to think about what we could do with the labeling....I'm concerned about waiting to get more data, how long is it going to get, to get the right number, whatever that right number is, if it's another thousand, or 5,000, or 10,000, to get to the answer. I don't think we know what that answer is going to be. It might be a little better to get to it, and a little faster to get to it and be able to settle this in phase 4 than in doing another phase 3, and then having to come back. I'm really concerned about having some tools in our toolbox.... (p.341)</p> <p>DR. GRIPSHOVER (committee, <b>voted yes</b>): I voted yes, but I also echo that it was more like maybe, or partial might even be a better way. I think that when I'm thinking of the risk-benefit, for oral, I actually think it's more important for oral. We don't have any good oral therapy for community-acquired pneumonia....whereas for IV, we still can do a beta-lactam and another macrolide. So we have the -- and the IV formulation also looked more toxic. So maybe if we started it with a oral and collected more data on that, with a phase 4,</p>

Committee	Year	Drug name	Comments
			<p>we could then feel more comfortable going with IV as one strategy. That's what I was thinking. (p.342)</p> <p>Dr. Green (committee, <b>voted no</b>): ...Having said that, I actually asked a question which could have swayed my vote. I was trying to give the sponsor a potential out because they were putting this great surveillance in place. And so I asked them, what level of signal will make you pause, make you stop, make you hold, make you withdraw, and I couldn't get an answer. If they would have told me one or two cases would make them pause, I could have voted yes with an understanding that they would try to work out some sort of an understanding with the FDA.... (p.346)</p> <p>....</p> <p>Dr. Baden (committee, <b>voted yes</b>): So you have a split decision from the committee, however, in hearing the themes, it's not clear to me that it's a split decision. I hear much more of a continuous decision and where one falls on that risk-benefit with the challenges of antibiotic, the unmet medical need, the potential for postmarketing surveillance; labeling and strengthening pharmacovigilance being one way to mitigate and manage the potential benefit, and then the issue of the signal is just too concerning and needs to be better characterized before you can accept that benefit. (p.352)</p> <p>....</p> <p>Dr. Daskalakis (committee, <b>voted no</b>): I voted no, which was really a no on the side of maybe, mainly because of the fact that we don't really have the full story of hepatotoxicity. .... a vote for no for this question is not necessarily a vote for no for recommending approval. That's not what this question asks. So, I put that out there to say that I vote for no with the idea that potentially being very stringent if this drug is recommended for approval since we do need new antibiotics, especially oral antibiotics for these conditions that reduce the risk of some of the other complications of fluoroquinolones. I think that it's critical that the, again, phase 4 studies are very rigorous and very clear. And I also want to bring up the idea of is this a place where we think about a REMS, where we create something where we realize that there's an associated risk with the drug, and that we give some tool to be able to allow patients to access it, but shift the risk balance by creating some sort of clear documentation that this is a piece of the story of this drug as you use it in your practice. (p.348)</p> <p>DR. LEE (temporary voting member, <b>voted yes</b>): Will Lee. Yes. This was a very agonizing vote. ....the FDA's been incredibly risk-adverse with one exception, and that's cancer drug. .... So since 1999, there's been essentially nothing, not even telithromycin. It never was withdrawn except eventually by the company. So FDA has not withdrawn a single drug since 1999 because I think they've been relatively risk-averse. Now, this drug clearly has a strong hepatotoxicity signal, however, I think we heard Dr. Fernandez say that it took there and a half years to get 880 patients. My concern is that we keep discouraging companies from going forward. Perhaps the FDA has to come up with something different, a provisional approval with the understanding that we're in the post-Ketek world, we're in the post -- we're 18 years since 1999, and we have to come</p>

Committee	Year	Drug name	Comments
			up with a new strategy to allow the phase 4 studies to go forward. We have much better pharmacovigilance, presumably, all these huge databases that we and raw from. And I think we need to come up with somehow a better paradigm, maybe stronger labeling but also perhaps some way to acknowledge. The C. diff issue is huge, the quinolone resistance issue is huge, and the potential death from the primary disease is huge. We've got to be able to figure out where the balance is. (p.349)
Cardiovascular	8/5/2013	Tolvaptan, NDA #204441, NME, Priority, Orphan	<p><b>River toxicity was a big issue. Some committee members who voted yes felt that postmarketing REMS and study could manage the risk when stating their rationales for approval. Unclear evidence on the role of PMS.</b></p> <p><b>Votes: yes 6 no 9</b></p> <p><b>Approval: rejected by the FDA</b></p> <p>DR. MCQUADE (sponsor): In addition, as I mentioned before, we will initiate a postmarketing patient registry to collect monthly liver monitoring results on tolvaptan treated outpatients to better understand the risks and assess additional actions. (p.90)</p> <p>....</p> <p>We look forward to potentially working with the DILIN Network to provide data on patients with hepatotoxicity in the postmarketing environment. And we're committed to additional research to further understand the genetic, biochemical, and metabolic factors that may be predictive of the hepatotoxicity. We want to continue our commitment to the field as tolvaptan approaches the postmarketing environment. The first is to commit to the postmarketing patient registry that I suggested earlier to provide greater insight into the risk of injury. The second is to take the ongoing study,..... Finally, while we do not believe a study in CKD4 is necessary for the treatment of patients in early disease, we will commit to conduct such a study to measuring of the time to a doubling of serum creatinine or ESRD and to address this empirical question. (p.94-95)</p> <p>....</p> <p>Dr. Orza (voting member, consumer rep, <b>voted no</b>): So my question I guess is for the FDA. To what extent do you think you could satisfactorily address all the questions that we have about the real effect and the safety signal through a registry versus a trial? (p.179)</p> <p>Dr. Thompson (FDA): On the efficacy side, I don't think that just following patients in the registry is going to give you tremendous insight into tolvaptan's efficacy and providing what could be a very important benefit, and a benefit that we need to have a good understanding of to make sure that we act appropriately in terms of how burdensome the REMS is, if we withdraw the drug from the market if something very bad were to happen. So I think it's only really with controlled clinical trials that we're going to get a better understanding of the true nature of the benefit that we're going to weigh against this risk. (p.180)</p> <p>...</p> <p>DR. MCQUADE (sponsor): In terms of when to stop, I think that's a more difficult question. I don't particularly have a good answer right</p>

Committee	Year	Drug name	Comments
			<p>now. I think that that's part of the reason why we would agree with FDA that if we were to put this drug on the market, we would agree to do a post-approval study.... (p.309)</p> <p>....</p> <p>DR. ORZA (voting member, consumer rep, <b>voted no</b>): The question is about if this drug were approved, what would that do to our ability to have another trial, in terms of the ethics of another placebo-controlled trial?</p> <p>Dr. Temple (FDA): Well, they're planning one in a sicker population already.</p> <p>DR. LINCOFF (committee, <b>voted yes</b>): I think we also have to recognize that we're not going to get from postmarketing registry data efficacy....I think you can't get safety because you can get event rights. But if we're really concerned about efficacy, then we need to do more trials. In a disease like this that is as substantial, variation, et cetera, there's no way to assess what without a control group. (p.398)</p> <p>...</p> <p>DR. MORRATO (committee, <b>voted yes</b>): I voted yes....For me, the unmet medical need was significant....I found the clinical significance of the efficacy findings less than I'd like to see, but I was satisfied and was clear there was risk of life-threatening, drug-induced liver injury that exceeds the threshold typically used for market withdrawal. However, I believe the REMS program was appropriate, given the risk and prior precedent.... And it was a difficult decision, but I ultimately try to be flexible in considering the totality of the data, the medical need, and the rigor of the REMS. So I voted in favor of drug approval. (p.400-401)</p> <p>Dr. Proschan (committee, <b>voted no</b>): I voted no....Perhaps if they had already had a trial and only needed one trial at .05, I might have voted differently. (p.402)</p> <p>Ms. Broyles (voting member, consumer rep, <b>voted yes</b>): I voted yes... I think to dismiss all the comments and testimony of all those, the patients that actually are living with it, is difficult. And I think that ultimately it is the patient's decision if they can't comply and can't fulfill the needs. But I think having the REMS program in place will certainly help that. (p.406)</p> <p>DR. CHALASANI (committee, <b>voted yes</b>): Naga Chalasani. I voted yes... Potentially pretty bad events could happen. But I thought it was manageable as was proposed by their REMS program.</p> <p>Dr. Kliger (committee, <b>voted yes</b>): I voted yes. On the risk side, I'm troubled by the potential of substantial liver toxicity, but it seemed to me that the only way to know that is to follow it carefully with an appropriate registry and collect real data to see what the real risk is. (p.409)</p>

## **Appendix N for Study 3: PMS discussions and approval decisions by safety and efficacy (period 2)**

In period 2, I was able to identify 20 meeting agendas (20 new indications for 16 drugs) that had only efficacy PMR/PMCs or only safety PMR/PMCs. When we compare voting results and PMR/PMCs attached with approval by safety and efficacy, we might be able to find where the role of PMS on approval process is larger. For example, if we find the percentage of votes for approval is much higher for drugs with safety issues when PMS was discussed in relation to approval than the percentage of approval votes for drugs with efficacy issues, the tradeoff lies in safety issues not efficacy.

Other than confirmatory trials for accelerated approvals, field study for animal rules, and pediatric studies that are required by law, postmarketing efficacy studies are rare. The data I have didn't say much about efficacy. Only 6 drugs (6 new indications--one indication per drug) in Period 2 had only efficacy postmarketing studies (the main issue was efficacy for these drugs): 5 of them were accelerated approvals and the other one was regulated by animal rule<sup>231</sup>. For accelerated approval cases, it is hard to disentangle the effect of the discussion on PMS in the context of approval on voting for approval. The animal rule case, raxibacumab, had no voting.

Let us look at the safety postmarketing studies. Among 14 new indications (10 drugs) that eventually had safety postmarketing studies (safety only), two had discussions on PMS in relation

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<sup>231</sup> FDA's regulations concerning the approval of new drugs when human efficacy studies are not ethical and field trials are not feasible are codified in 21 CFR 314.600 through 314.650 for drugs and 21 CFR 601.90 through 601.95 for biological products. Approval of a drug under the Animal Rule imposes a requirement for postmarketing studies: Postmarketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and the drug is used).

to approval—adalimumab and teduglutide recombinant. The average vote for approval in those two drugs was 94% when the committee discussed PMS and approval. For 12 other meeting agendas without PMS-approval discussion, the average vote for approval was 92%. The percentage of approval votes was higher when PMS-approval was discussed, but the difference is trivial.

Another way to examine where the main tradeoff happens is to compare votes for safety and efficacy (separately) with votes for approval. However, not many meetings had separate questions on safety and efficacy: only three were identified. Solithromycin had safety issue: only 8% voted yes to safety while 100% voted for efficacy. There was discussion on PMS and approval, but in the end, 54% voted for approval. The FDA rejected application.

In case of vedolizumab with efficacy issue, all committee voted yes for safety but 57% voted yes for efficacy. The majority of committee (95%) voted for approval. But, the FDA decided to focus on safety issues when it comes to postmarketing studies. In case of bedaquiline, all committee voted yes to efficacy and 61% voted yes to safety. There was no voting for weighing the balance or recommending approval for bedaquiline. FDA approved this drug with mainly safety postmarketing studies.

**Table N-10. Drugs that had separate voting questions, Period 2**

Drug name	PMS-approval discussion	Votes for approval	Votes on safety	Votes on efficacy	FDA approval decision
vedolizumab	No	95%	100%	57%	Approved with PMS (4 PREA, 1 FDAAA safety, and 5 safety PMC)
solithromycin	Yes	54%	8%	100%	Rejected
bedaquiline	no	No voting	61%	100%	Approved with PMS (6 FDAAA safety studies, 1 accelerated approval confirmatory trial, 2 PMC for data submission)

The vast majority of efficacy trials belong to confirmatory trials (accelerated approvals), PREA studies, and animal efficacy studies that are required by law regardless of their issues. For safety concerns, the difference was insignificant. Not much conclusion can be made from the currently available data.

## Appendix O for Study 3: The role of PMS in addressing uncertainties, for successful applications

The following table shows the concerns raised by advisory committees during 2012-2016 for drugs that won approval (when first submitted) after the meeting. This table was created to see in how many cases PMS played roles in addressing the issues/concerns, which could tell us if PMR/PMCs had some roles in addressing uncertainties.

**Table O-11. The role of PMS in addressing uncertainties**

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
ZINPLAVA BLA #761046 Antimicrobial "First-in-class"	6/9/2016 63%	Mechanism of action of the drug was unclear and uncertain about the endpoint as optimal for primary efficacy analysis. Some concerns on lack of substantial evidence on efficacy.  FDA was concerned about the uncertainties in assessing any potential negative impact on clinical cure of CDI and the safety signal for cardiac failure.	<b>No role of PMS</b>	10/21/2016 Approved with 1 PREA for <u>modified</u> <u>indication</u>



Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
IMLYGIC BLA #125518 Oncologic	4/29/2015 96%	<p>There was extensive discussion, with no clear consensus, regarding whether the efficacy of IMLYGIC was limited to a definable subset of the Study population (e.g., those subjects with less advanced disease).</p> <p>In FDA review document, FDA says “The risk of shedding, including the risk of transmission of infection to close contacts and healthcare providers, will be assessed in two postmarketing studies. Thus, although patients with advanced melanoma may have a life-threatening disease, and IMLYGIC has not been shown to have an effect on survival, the benefits of IMLYGIC are clinically meaningful and may be important for many patients.”</p>	<b>Some role of PMS in reducing uncertainties</b>	10/27/2015 Approved with 2 FDAAA studies (the risk of herpetic infection and bio-distribution and shedding of Imlygic)
CRESEMBA NDAs #207500, 207501 Antimicrobial	1/22/2015 no vote (For the question of substantial evidence, 100% voted yes for aspergillus and 73% for mucormycosis)	<p>Several members noted the need for therapeutic drug monitoring and more study on QT interval, and drug interactions.</p> <p>For the indication of mucormycosis, the committee was hesitant because the data depended on historical controls and no direct comparison with AmphotericinB. Several mentioned a critical need for PMS and one of the two who voted no expressed concern that if FDA sets the bar this low for a “secondary” approval, it will be flooded with “primary” approvals for drugs that will reach the market that shouldn’t. The other who voted no asked for a better comparison of death rate.</p>	<p>The PMRs are not relevant to the major concerns raised by the AC. The PMC, patient registry, might be relevant for drug monitoring.</p> <p><b>Unclear, but, if any, very limited role of PMS in addressing uncertainties</b></p>	3/6/2015 approved with 3 FDAAA studies (5-year susceptibility study, two carcinogenicity studies) and 1 PMC (registry for patients who have invasive mucormycosis or non-fumigatus aspergillus)

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
SIVEXTRO NDA #205435, 205436 Antimicrobial	3/31/2014 100%	One member noted that it should not be approved for the 12-18 year old age range. Several expressed the need for pediatric information and drug interaction. One member recommended FDA use care when determining the microbiological profile in the labeling. Resistance development was also discussed.	<b>Some role of PMS in addressing uncertainties</b>	6/20/2014 approved with 5 PREA studies (12-18 yrs old) and 1 FDAAA (5-year drug resistance surveillance study)
DALVANCE NDA #21883 Antimicrobial	3/31/2014 100%	The committee recommended that labeling should indicate that the drug is not for pediatric use. Caution with liver disease, need for exploring the microbiological profile, drug resistance, and long-term safety studies were mentioned.	FDAAA studies (5-year drug resistance surveillance study and defining mechanism of resistance). <b>Some role of PMS in addressing uncertainties</b>	5/23/2014 approved with 4 PREA studies, 2 FDAAA studies, and 2 PMCs (preparing for Master Cell Bank and batch test)
AVYCAZ NDA #206494 Antimicrobial	12/5/2014 92%	Some recommended the final vetting of Phase 3 data and mandatory phase 4 study in patients with resistant pathogens. Most committee were concerned about the mortality and renal-impaired patients. A therapeutic dose monitoring and REMS was also discussed.	FDAAA studies: (1) 5-year prospective study for susceptibility (2) PK, safety, clinical outcomes in patients with renal impairment. <b>Some role of PMS in addressing uncertainties</b>	2/25/2015 approved with 3 PREAs and 2 FDAAA studies.
IMPAVIDO NDA #204684 Antimicrobial  "First-in-class"	10/18/2013 94% for visceral leishmaniasis, 88% for cutaneous leishmaniasis, and 81% for mucosal leishmaniasis	The following concerns were discussed: Lack of data on those < 75kg and under 12 years, use of contraception for at least 4-5 months post therapy, the risk of relapse, differences in efficacy in children, selection bias in the single-arm study, and not all leishmaniasis are the same. Also, sperm and QT analyses was discussed.	FDAAA studies: (1) pregnancy outcome, 10 years (2) QT interval (3) effect on male hormones and spermatogenesis <b>Some role of PMS in addressing uncertainties</b>	3/19/2014 approved for all three indications with 3 FDAAA studies and 1 PMC (descriptive safety and efficacy in weight > 75kg)

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
Levaquin sNDAs #20634/61, 20635/67, 21721/28 Antimicrobial  Animal rule	4/4/2012 100%	Also in Appendix Q.  Concerns on susceptibility data, the need for study infants under 6 months were expressed.  Animal rule was applied, and it requires postmarketing studies such as field study on humans.	This was supplemental approval. Safety was established postmarketing.  <b>No role of PMS in addressing uncertainties other than Animal rule PMS.</b>	4/27/2012 approved with 1 PMR (Animal rule) – a field study in case of bioterror attack in the US
RAXIBACUMAB BLA #125349 Antimicrobial  “First-in-class” Animal rule	11/2/2012 100%	Also in Appendix Q and Appendix M. Potential interaction with anthrax vaccines, dosing by weight, doses > 40mg/kg, effective dosing during different stages of disease progression, infusion times/more concentrated infusion, and uncertainty on safety in patients with anthrax were discussed. The committee also raised concern regarding whether concurrent use of raxibacumab and anthrax vaccination may impact vaccination efficacy.	Unclear role of PMS on approval.  <b>Some role of PMS in addressing uncertainties other than Animal rule PMS.</b>	Approved on 12/14/2012 with 1 Animal Rule PMR (field study on Bacillus anthracis) and 1 PMC (immunogenicity)
SIRTURO NDA #204384 Antimicrobial  Accelerated approval	11/28/2012 no vote	The committee agreed to lack of evidence to support traditional approval due to unclear clinical endpoints. Concerns shared includes: specific population (HIV, blacks, children, etc.), mortality, cardiotoxic and hepatotoxic effects, QT interval, etc.	A confirmatory trial were required 6 FDAAA studies: (1) long-term registry for safety (2) (3) (4) quality control and in-vitro (5-year) studies (5) transporter study (6) DDI  <b>Some role of PMS in addressing uncertainties</b>	12/28/2012 Approved with 1 confirmatory trial for AA, 6 FDAAA safety PMRs, and 2 PMCs (submit the results of ongoing trials)
SAVAYSA NDA #206316 Cardiovascular	10/30/2014 90%	Issues raised: dosing for normal renal function and separating out ischemic and hemorrhagic stroke	<b>No role of PMS in addressing uncertainties</b>	1/8/2015 approved with 2 PREA studies
ZONTIVITY NDA #204886 Cardiovascular  “First-in-class”	1/15/2014 91%	Issues raised: risk of bleeding, lack of an antidote, safety in patients < 60kg, and development of weighted, composite, quantitative assessments of safety and efficacy	<b>No role of PMS in addressing uncertainties</b>	5/8/2014 approved without PMS

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
ADEMPAS NDA #204819 Cardiovascular  "First-in-class"	8/6/2013 100%	Issues: unknown safety for patients with a history of coronary artery, misuse of drug, need for the distribution of hemodynamic responses of the patients to ensure that it was not a small percentage of very responsive patients driving the results.	<b>No role of PMS in addressing uncertainties</b>	10/8/2013 approved without PMS
PHENYLEPHRINE HYDROCHLORIDE NDA #203826 Cardiovascular	9/13/2012 20%	See appendix M – PMS-approval discussion  The need for true outcome data in the settings of shock, additional longer-term use and additional criteria, adequately characterized safety profile, and collecting data in general anesthesia were addressed.	Some role of PMS in approval was recognized by a member.  <b>No role of PMS in addressing uncertainties</b>	Approved on 12/20/2012. A PREA study was required—a trial for 12-16 years old patients
OCALIVA NDA #207999 Gastrointestinal  Accelerated approval	4/7/2016 100%	Unanimously agreed to support accelerated approval. The committee suggested studies for this drug as monotherapy, PK profile of this drug, long-term safety studies, better characterization of hepatic adverse events, monitor HDL, etc.	Confirmatory trials were required and they address the issues raised during the meeting. <b>Some role of PMS in addressing uncertainties</b>	5/27/2016 accelerated approval with 3 confirmatory trials (PMRs) and 1 PMC (formulation of dose for hepatic impaired)
ENTYVIO BLA #125476, 125507 Gastrointestinal	12/9/2013 100% for UC and 95% for Crohn's	The committee shared some concerns: only one primary endpoint was met, the risk of PML and serious infection, immunogenicity, etc.	PMCs: (1) an ongoing trial for long-term safety for patients with UC and Crohn's, (2) observational pregnancy, (3) milk only lactation study, (4) immunogenicity, and (5) disease-DDI <b>Some role of PMS in addressing uncertainties</b>	5/20/2014 Approved with 1 FDAAA requirement (observational, comparing with other IBD agents), 4 PREAs, and 5 PMCs

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
HUMIRA sBLA #125057/232 Gastrointestinal	8/28/2012 88% Supplemental	See appendix M – PMS- approval discussion  Concerns include: not fully established optimal dose, dose > 40mg, lack of long-term safety evaluation for this specific indication, decreased QALY and need for alternative therapy	Recognized role of PMS in approval  FDAAA studies: (1) genetic mutation (2) long- term safety and efficacy in UC (3) anti-adalimumab antibody assay (4) immunogenicity (5), (6) safety and PK for dose > 160/80mg  <b>Some roles of PMS in addressing uncertainties</b>	Approved on 9/28/2012. 6 FDAAA and 1 PMC (pediatric trial)
GATTEX KIT NDA #203441 Gastrointestinal  “First-in-class”	10/16/2012 100%	See appendix M – PMS- approval discussion  Concerns discussed: QALY, morbidity and mortality, the need for nutritional metabolic data and longer-term safety data, liver function, pancreatic enzyme level, and REMS.	No clear evidence of the role of PMS in approval  <b>Some roles of PMS in addressing uncertainties</b>	Approved on 12/21/2012 with 1 FDAAA on long-term observational safety
PORTRAZZA BLA #125547 Oncologic	7/9/2015 54%	See appendix M – PMS- approval discussion  Committee members were concerned about the toxicity of hypomagnesemia, potential over-anticoagulation in deaths, and venous thromboembolic events.	Mixed views on PMS  No PMS— <b>no role of PMS in addressing uncertainties</b>	Approved on 11/24/2015 without PMR/PMCs
ZARXIO (NEUPOGEN?) BLA #125553 Oncologic	1/7/2015 100%	Uncertainty about the accuracy of data—subgroup of population and lack of data on rare adverse effects	<b>No role of PMS in addressing uncertainties</b>	3/6/2015 Approved with 1 PREA study
FARYDAK NDA #205353 Oncologic  Accelerated approval	11/6/2014 29%	See Appendix Q. Concerns and issues shared: lack of data on other endpoints—overall survival or QALY, toxicity and uncertain magnitude of PFS improvement, finding a population that could benefit from this treatment  REMS was assigned	Confirmatory trials were required to reduce uncertainty in clinical benefit  <b>Some role of PMS in addressing uncertainties</b>	2/23/2015 Accelerated approval with 2 confirmatory trial requirements (a phase 2 study with overall response, and phase 3 study with PFS)

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
TRIFERIC NDA #206317 Oncologic	11/6/2014 73%	See appendix M – PMS- approval discussion  Artificial settings of trials were of concerns, thus uncertainty in translating the conclusions to the practice. Dosing issue was also raised. The committee generally agreed that additional studies are necessary to establish the efficacy of the drug to reduce the dose of the comparator (a larger, randomized trial).	No evidence on the role of PMS in approval  <b>No role of PMS in addressing uncertainties</b>	Approved on 1/23/2015 with 2 PREA studies
LYNPARZA NDA #206162 Oncologic  Accelerated approval	6/25/2014 15% (the committee recommended FDA to wait until the result)  FDA approved this drug for a different indication on 12/19/2014	The majority of the committee voted no and shared concerns including (1) lack of data on outcomes of subsequent chemotherapy, (2) the occurrence and duration of adverse effects including secondary cancer, (3) overall survival rather than just PFS and additional QALY data	FDAAA studies address concerns and uncertainties raised by AC  <b>Some role of PMS in addressing uncertainties</b>	12/19/2014 Approved with 2 confirmatory trials for AA and 3 FDAAA safety requirements (case studies on myelogenous leukemia / myelodysplastic Syndrome, 2 ongoing trials on renal and hepatic function)
PERJETA sBLA #125409/51 Oncologic  Accelerated approval	9/12/2013 93%	Issues and concerns raised: uncertainty about long term clinical benefit, problems with pCR as an endpoint, uncertainty about duration of treatment, and cardiac toxicities	FDAAA study address concerns and uncertainties raised by AC  <b>Some role of PMS in addressing uncertainties</b>	9/30/2013 Approved with 1 confirmatory trial for AA, 1 FDAAA (cardiac safety), and 2 PMCs (final report on EFS and pretreatment molecular subtyping of tumors)
Votrient sNDA #22465/010 Oncologic	3/20/2012 85%	The marginal effect observed didn't present clinical benefit. Judgement on whether or not 3- month improvement in PFS in advanced STS patients. Data didn't suggest QALYs.	No PMS was attached to the approval <b>No role of PMS</b>	4/26/2012 Approved without PMS

Drug	Meeting/ votes	Concerns raised by AC	The role of PMS in addressing uncertainties raised by AC	Final approval decision
Marqibo NDA #202497 Oncologic  Accelerated approval	3/21/2012 54%	<p>Uncertainty about the benefit of the formulation and the quality of data as well as the feasibility of the phase 3 trial (confirmatory trial) in patients &gt; 60 yrs that is crucial was raised.</p> <p>OSE was concerned about numerous safety issues regarding the preparation of Marqibo and the labeling instructions.</p>	<p>Confirmatory trials were required to reduce uncertainty in clinical benefit. Negotiated PMCs address safety issues raised by FDA staff</p> <p><b>Limited role of PMS. Concerns on preparation were addressed through labeling and PMS</b></p>	8/9/2012 Approved with 1 confirmatory trial for AA (patients with ALL > 60 years) and 2 PMCs (preparation of drugs, simplification of the preparation)
Kyprolis NDA #202714 Oncologic  Accelerated approval	6/20/2012 92%	<p>Concerns shared include cardiac safety and one single-arm study was the basis for decision.</p> <p>Committee members consistently stated that their comfort was increased by the additional phase 3 trial which is ongoing.</p>	<p>Confirmatory trials for <b>accelerated approval</b> were required to reduce uncertainty in clinical benefit, and FDAAA studies address part of issues raised by AC</p> <p><b>Some roles of PMS in addressing uncertainties</b></p>	7/20/2012 Approved with 1 confirmatory trial for AA and 6 FDAAA PMRs (a RCT for cardiac toxicities, a RCT for pulmonary toxicities, safety at dose 20/56, hepatic safety, and renal impairment)

Notes:

1. DDI: drug-drug interaction.
2. QALY: quality of life years
3. UC: Ulcerative Colitis
4. PK: Pharmacokinetics
5. QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle in cardiology
6. PFS: Progression Free Survival
7. EFS: Event Free Survival
8. OS: Overall Survival
9. DFS: Disease Free Survival
10. OSE: The Office of Surveillance and Epidemiology at the FDA
11. STS: Soft Tissue Sarcoma
12. ALL: Acute lymphocytic leukemia

## Appendix P for Study 3: The role of PMS in addressing uncertainties, for re-submitted application

The following table shows the issues raised by FDA before rejecting approval and FDA's final decisions on approval and PMR/PMCs. The sample includes 5 drugs, among those were discussed in advisory committee meetings during 2012-2016, whose approvals were rejected when first submitted. In this way, we can find evidence whether or not PMR/PMCs did play some role of reducing uncertainty that was part of the rationale for rejection. I added some discussions of AC meetings for two drugs—Kengreal and Northera—that had two committee meetings in order to see if the committee discussions reflect what has been changed.

**Table P-12. Rationale for rejection and FDA's final decisions on approval and PMR/PMCs**

Drug	Approval decision	Issues (reasons for rejection when first submitted)	The role of PMS in resolving issues
Byvalson, NDA #206302, Cardiovascular	Meeting: 9/9/2014 (40% votes)  Approval: 6/3/2016	On letter 12/24/2014, FDA said that a new combination should contribute meaningfully to the effect achievable with the individual agents (or to combinations fewer agents) or a safety advantage, but this drug failed to demonstrate them. FDA asked the firm to develop a more compelling case for the drug compared with high dose nebivolol. FDA also said that they would be willing to consider approval of the lower dose, even absent demonstration of better tolerability, if the firm shows that Byvalson doses are about as additive as are other combinations one might expect to be more mechanistically independent.	In 2014, AC discussed nebivolol/valsartan combination (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg). In 2016, 5 mg/80 mg tablets were approved. <b>No PMS</b> were required or agreed. <b>No role of PMS on reducing uncertainty.</b>



Drug	Approval decision	Issues (reasons for rejection when first submitted)	The role of PMS in resolving issues
Kengreal, NDA #204958, Cardiovascular	<p>First Meeting: 2/12/2014 (22% votes for PCI, 0% for BRIDGE indications)</p> <p>Second meeting: 4/15/2015, (82% votes for approval for PCI, no question on BRIDGE indication)</p> <p>Approval: 6/22/2015</p>	<p>On the letter 4/30/2014, FDA doubted about clinical relevance: some subcomponents of the primary endpoint may not represent clinical benefit, lack of documentation, and missing data in PCI indication. Sensitivity analyses and documentation were requested. For BRIDGE indication, a new study was suggested. CMC and bioequivalence issues were raised. There were uncertainties about the data relevance to American practice and the data support use of cangrelor as an adjunct to PCI.</p> <p>During the AC meeting on 2/23/2012, some concerned about (1) dosing due to the protocol with uncertainty, (2) risk of MI—uncertainty as to whether reduction in risk was clinically important, (3) the design of a major trial and negative results from two trials, and (4) approving a drug based on PK data without clinical trials.</p> <p>In the second meeting in April 2015, some still were concerned that efficacy data only came from one trial and two trials failed, and there was uncertainty about subgroup due to small numbers.</p>	<p>In June 2015, it was approved as an adjunct to PCI. <b>No PMR/PMCs</b> were attached to the approval. <b>No role of PMS on reducing uncertainty.</b></p>
<p>Northera NDA #203202, Cardiovascular</p> <p>“First-in-class” Accelerated approval</p>	<p>First Meeting: 2/23/2012 (58% votes for yes)</p> <p>Second meeting on 1/14/2014 (94% votes for approval)</p> <p>Approval: 2/18/2014</p>	<p>3/28/2012 FDA letter says there were issues in clinical/statistical matters. 1 out of 3 studies was positive and the results of the two studies undercut the successful study. None of the submitted studies show durability of effect beyond one week. A study designed to demonstrate durability of effect over a 2- to 3-month period was recommended.</p> <p>During the first meeting in February 2012, the committee expressed concerns regarding uncertainty about measurement of effect, limited randomized data on duration, and lack of safety data. The sponsor proposed a PM observational registry of 200-300 patients over 4-5 years to obtain more data—committee members would like to see more data, but the design should be further determined.</p> <p>During the second meeting in 2014, the majority of the committee agreed that it should be approved. The robust efficacy data, reasonable study design, and convincing long-term data (15 years in Japan) were mentioned. Some members noted that it should be approved under accelerated approval so that it can be studied long term effect, and training for prescribers were recommended.</p>	<p>In response to FDA, the applicant submitted a new Study 306B, a study of subjects with Parkinson's disease that was re-engineered with a dizziness endpoint.</p> <p>In 2014, this drug was approved as accelerated approval with 1 PMR (confirmatory trial) that measures sustained effects. The <b>PMR (accelerated approval) played role in decreasing uncertainty.</b></p>

Drug	Approval decision	Issues (reasons for rejection when first submitted)	The role of PMS in resolving issues
Tobi Podhaler, NDA #201688, Antimicrobial	Meeting: 9/5/2012 (93% votes)  Approval: 3/22/2013	10/19/2012 letter indicates that facility inspection failure was the main reason for rejection.  During the AC meeting on 9/5/2012, the committee did not find major concerns regarding labeling; one panel member voted no because the data was too limited to show long-term safety and recommended a longitudinal study. But, long-term safety wasn't the issue of rejecting approval.	3 FDAAA safety studies (an observational study for decreasing susceptibility, a 1-year observational cohort study for comparing with other drugs, a human factor study) and 1 PMC (create/update instructions) were identified. <b>No to little role of PMS on reducing uncertainty</b>
Vibati, NDA #22407, Antimicrobial	Meeting: 11/29/2012 No voting for approval or weigh risk/benefit, but the AC was asked to vote whether the data provided substantial evidence for safety and efficacy for VAP and 40% voted yes, and for NP 87% voted yes for evidence. The first AC meeting was held on July 2008, but data are not available.  Approval: 6/21/2013	On the letter of 11/23/2009 (the first round of application), FDA rejected approval because (1) 2 phase III trials do not show substantial evidence for NP indication (AC meeting was held on July 2008); (2) the published literature doesn't permit interpretation of non-inferiority for VAP indication; and (3) lack of mortality data. FDA suggested (1) all mortality data, (2) new study for NP, and (3) more data and rationale for VAP.  On letter 12/21/2010, FDA rejected again because of lack of evidence for NP and non-inferiority, uncertainty about target population (due to methods of chest radiography), inadequate analysis method comparing with historical studies, inadequate pooling analysis, and unclear diagnosis of renal failure. FDA requested two additional trials. On 2/23/2013 (three months after the second AC meeting on 11/29/2012), FDA rejected approval again for CMC/facility issues.	This drug was approved for VAP on June 2013. REMS and 3 PREA studies were required at approval.  <b>No role of PMS on reducing uncertainty.</b>

## Appendix Q for Study 3: Examination of accelerated approvals and animal efficacy approvals

9 drugs with accelerated approval and 2 drugs with animal rule approvals in the sample

**Table Q-13. Examination of accelerated approvals and animal efficacy approvals**

Drug	Approval decision	Issues	The role of PMS
Rociletinib  "First-in-class" Accelerated approval	AC: 4/12/2016 Votes: 8%  Rejected (not approved)	The updated data shows lower response rate than initially reported <sup>232</sup> <sup>233</sup> . The committee recommended the FDA to wait until the phase 3 trial result comes due to high uncertainty (lack of data, variable PK, lack of power, etc.) The sponsor stopped all on-going investigations and withdrew its application. The sponsor was also facing federal probe on data for the drug—\$20M settlement with SEC was offered by the sponsor in August 2, 2018.	This drug had <b>high uncertainties</b> and lower response rate than expected. <b>No role of PMS in approval process</b>
Droxidopa / Northera  "First-in-class" Accelerated approval	1 <sup>st</sup> AC: 2/23/2012 Votes: 58% 2 <sup>nd</sup> AC: 1/14/2014 Votes: 94%  Rejected when first submitted, but approved after the 2 <sup>nd</sup> meeting  <u>Approved for slightly modified indication</u>	Also in Appendix P. 3/28/2012 FDA letter says there were issues in clinical/statistical matters. 1 out 3 studies was positive and the results of the two studies undercut the successful study. None of the submitted studies show durability of effect beyond one week. A study designed to demonstrate durability of effect over a 2- to 3-month period was recommended. "Worrisome" safety signals in test results and post-marketing cases in Japan.  During the first meeting in February 2012, the committee expressed concerns regarding uncertainty about measurement of effect, limited randomized data on duration, and lack of safety data. The sponsor proposed a PM observational registry of 200-300 patients over 4-5 years to obtain more data—committee members would like to see more data, but the design should be further determined.  During the second meeting in 2014, the committee agreed the robust efficacy data, reasonable study design, and convincing long-term data (15 years in Japan). Some members noted that it should be approved under accelerated approval so that it can be studied long term effect. <u>Efficacy evidence</u> : 4 clinical studies	When second submitted, the majority issues were addressed with additional data from a new study. It seemed the FDA had debates internally—there was a strong argument for both approval and rejection.  FDA decided to approve and added: "the existence of prior studies that failed to show durability of treatment effect essentially make the short-term demonstration of efficacy reasonably unlikely to predict a long-term treatment effect here."  1 AA confirmatory trial that measures sustained effects was required. The <b>PMR played some role in decreasing uncertainty</b> .

<sup>232</sup> <https://www.onclive.com/web-exclusives/clovis-ends-development-of-rociletinib-in-lung-cancer>

<sup>233</sup> <https://www.biospace.com/article/federal-agencies-want-to-know-more-about-clovis-oncology-s-rociletinib-data-from-last-fall-/>

Drug	Approval decision	Issues	The role of PMS
Olaparib / Lynparza  Accelerated approval	AC: 6/25/2014 Votes: 15% (the committee said it should be detailed until the result comes)  This drug was approved for a different indication on 12/19/2014	Also in Appendix O. The majority of the committee voted no and shared concerns including (1) lack of data on outcomes of subsequent chemotherapy, (2) the occurrence and duration of adverse effects including secondary cancer, (3) overall survival rather than just PFS and additional QALY data  <u>PMS</u> : Approved with 2 confirmatory trials for AA and 3 FDAAA safety requirements (case studies on myelogenous leukemia / myelodysplastic Syndrome, 2 ongoing trials on renal and hepatic function) <u>Efficacy evidence</u> : single, non-RCT, a robust overall response rate with a clinically meaningful duration	The majority of the committee voted for a delay. After the AC and within the review cycle, the applicant submitted results and datasets to <u>support a different indication</u> .  <b>Some role of PMS in addressing uncertainties</b>
Panobinostat capsules / Farydak  Accelerated approval	AC: 11/6/2014 Votes: 29%  Approved	Also in Appendix O. "The main issues in this NDA are the uncertainty of efficacy findings due missing data and consequent censoring, and the toxicity of panobinostat used in combination with bortezomib and dexamethasone, leading to uncertainty of benefit as related to risk" (FDA)  Concerns and issues shared: lack of data on other endpoints—overall survival or QALY, toxicity and uncertain magnitude of PFS improvement, finding a population that could benefit from this treatment.  <u>PMS</u> : 2 confirmatory trial requirements (a phase 2 study with overall response, and phase 3 study with PFS) And, REMS was assigned <u>Evidence</u> : 1 RCT, 2 single-arm trials	The committee voted against approval for the proposed indication, but the committee viewed a narrower indication might work. FDA, in agreement with the AC recommendation, approved for <u>a narrower population</u> .  <b>Some role of PMS</b>
Pertuzumab Injection / Perjeta  "supplemental" Accelerated approval	AC: 9/12/2013 Votes: 93%  Approved	Also in Appendix O. Issues and concerns raised: uncertainty about long term clinical benefit, problems with pCR as an endpoint, uncertainty about duration of treatment, and cardiac toxicities.  <u>PMS</u> : Approved with 1 confirmatory trial for AA, 1 FDAAA (cardiac safety), and 2 PMCs (final report on EFS and pretreatment molecular subtyping of tumors) <u>Evidence</u> : 2 RCTs	<b>Some role of PMS in addressing uncertainties</b>
Vincristine Sulfate Liposomes / Marqibo  Accelerated approval	AC: 3/21/2012 Votes: 54% (Marginal support for approval by AC)  Approved	Also in Appendix O. Uncertainty about the benefit of the formulation and the quality of data. Uncertainty about the feasibility of the phase 3 trial (confirmatory trial) that is crucial.  <u>PMS</u> : Approved with 1 confirmatory trial for AA (patients with ALL > 60 years) and 2 PMCs (preparation of drugs, simplification of the preparation) <u>Evidence</u> : 1 Single-arm trial	Some of FDA staff concerns were addressed through labeling and PMS, but <b>limited role of PMS</b>

Drug	Approval decision	Issues	The role of PMS
Carfilzomib / Kyprolis  Accelerated approval	AC: 6/20/2012 Votes: 92%  Approved	Also in Appendix O. Concerns shared include cardiac safety and one single-arm study was the basis for decision. Committee members consistently stated that their comfort was increased by the additional phase 3 trial which is ongoing.  <u>PMS</u> : Approved with 1 confirmatory trial for AA and 6 FDAAA PMRs (a RCT for cardiac toxicities, a RCT for pulmonary toxicities, safety at dose 20/56, hepatic safety, and renal impairment) <u>Evidence</u> : 1 single-arm trial	<b>Some roles of PMS in addressing uncertainties</b>
Obeticholic Acid / Ocaliva  "First-in-class" Accelerated approval	AC: 4/7/2016 Votes: 100%  Approved	Also in Appendix O. Unanimously agreed to support accelerated approval. The committee suggested studies for this drug as monotherapy, PK profile of this drug, long-term safety studies, better characterization of hepatic adverse events, monitor HDL, etc. The most concerning is the potential of liver associated toxicity (FDA)  <u>PMS</u> : 3 confirmatory trials (PMRs) and 1 PMC (formulation of dose for hepatic impaired) <u>Evidence</u> : 1 phase 3 trial, supported by 2 phase-2 RCTs	<b>Some role of PMS in addressing uncertainties</b>
Bedaquiline / Sirturo  "First-in-class" Accelerated approval	AC: 11/28/2012 No voting  Approved	Also in Appendix O. The committee agreed to lack of evidence to support traditional approval due to unclear clinical endpoints. Concerns shared includes: specific population (HIV, blacks, children, etc.), mortality, cardiotoxic and hepatotoxic effects, QT interval, etc.  FDA noted that the safety findings of increased mortality, QT prolongation, and possibly more hepatic-related events makes the requested indication too broad.  <u>PMS</u> : A confirmatory trial were required and 6 FDAAA studies: (1) long-term registry for safety (2) (3) (4) quality control and in-vitro (5-year) studies (5) transporter study (6) DDI as well as 2 PMCs (submit the results of ongoing trials) <u>Evidence</u> : Two phase 2 RCTs	Due to the safety profile, FDA approved this drug for a narrower indication.  <b>Some role of PMS in addressing uncertainties</b>
Levaquin  "supplemental" Animal rule	AC: 4/4/2012 Votes: 100%  Approved	Also in Appendix O. Concerns on susceptibility data, the need for study infants under 6 months were expressed.  <u>PMS</u> : Animal rule was applied, and the drug was approved with 1 PMR (animal rule, a field study in case of bioterror attack). This was supplemental approval. Safety was established postmarketing. <u>Evidence</u> : animal studies	<b>No role of PMS in addressing uncertainties other than animal rule requirement</b>

Drug	Approval decision	Issues	The role of PMS
RAXIBACUMAB  Animal rule	11/2/2012 Votes: 100%  Approved	Also in Appendix O and Appendix M. Potential interaction with anthrax vaccines, dosing by weight, doses > 40mg/kg, effective dosing during different stages of disease progression, infusion times/more concentrated infusion, and uncertainty on safety in patients with anthrax were discussed. The committee also raised concern regarding whether concurrent use of raxibacumab and anthrax vaccination may impact vaccination efficacy.  <u>PMS</u> : 1 Animal rule and 1 PMC <u>Evidence</u> : animal studies	Approved on 12/14/2012 with 1 Animal Rule PMR (field study on Bacillus anthracis) and 1 PMC (immunogenicity).  <b>Some role of PMS in addressing uncertainties other than Animal rule PMR.</b>

## **Appendix R for Study 3: Analyses on Advisory Committee Meeting Transcripts**

This appendix provides analyses on advisory committee meeting transcripts using committee votes and FDA's approval decisions. Here, the questions are: (1) do postmarketing studies address uncertainties? In what cases?; (2) how do committees vote under uncertainty with PMS and without PMS?; (3) Does FDA approve more drugs with PMS under uncertainties?; and (4) Does the option of postmarketing studies affect approval process for drugs without alternatives or orphan drugs?

### **Conceptual framework**

#### ***Do postmarketing studies address uncertainties? In what cases?***

The effect of PMR/PMCs on the approval process can be partly addressed by answering the question whether and how much postmarketing studies reduce the uncertainties in the future. First, we can take a look at the drug applications that were rejected when first submitted but approved later after resubmission. This examination allows us to access the complete response letter (CRL) sent to the sponsors by the FDA—the letters inform the sponsors why their drugs were rejected. When the second submission didn't address all of the concerns mentioned in the CRLs, how much of the remaining uncertainties were addressed through PMS?

Furthermore, we can examine how much uncertainties were addressed through PMS among the drug applications that won approval when first submitted. From the meeting transcripts and risk benefit assessment in summary review by FDA, we could learn what uncertainties and

risk issues were raised. Then, we study whether PMR/PMCs associated with the drug address these particular issues.

Next, we will examine cases where there were disagreements on drug approval. There might be disagreement among the committee members or disagreement between the FDA and committees. When FDA approves drugs amidst disagreement, does FDA employ PMR/PMCs in order to reduce potential risks and uncertainties? To what extent?

Lastly, in cases where PMS are mandatory (accelerated and animal approval paths), would some drugs not be approved or delayed even with mandatory PMS? When does this happen and why aren't PMS sufficient to reduce uncertainties? The answer might tell us something about when the availability of PMS is not enough to change a decision.

### ***Uncertainties, PMR/PMCs, and “yes” votes (committee behavior)***

Although challenging cases are brought before the FDA committees, there are variations in the level of uncertainty about approval among the drug applications that committees discuss. If the FDA brought drug applications with less uncertainty to advisory committees, we expect that having the option of postmarketing studies at the time of approval would not play a significant role in drug approval. The option of postmarketing studies makes little difference in making approval decisions without ambiguity. If committees discussed postmarketing studies in the context of approval for a drug with relatively less uncertainty, the presence of such discussion may indicate that the drug has known or notable risk requiring attention. Thus, compared to drugs without issues, more negative votes would be observed in those drugs with discussion on postmarketing studies in the context of approval.



However, for drugs with more uncertainty, the committees would vote more “yes” with the possibility of postmarketing studies, if the option of postmarketing studies has any effect. For drugs with greater uncertainty, advisory committees might be more willing to recommend approval with postmarketing study requirements (“conditional”) compared to the cases without such requirements.

In addition, for drugs with more uncertainty, we can test whether discussion on postmarketing studies in relation to approval is associated with “yes” votes to a greater extent in Period 2 than in Period 1.

In order to look at the level of uncertainty, I classified efficacy evidence requirements for approved drugs in Period 2 (due to data availability, drugs in the 1980s were not included in this analysis). In doing so, I adopted the classification method for efficacy evidence requirement flexibility from Sasinowski (2012) and Sasinowski et al. (2014). Sasinowski and his colleagues developed three classifications<sup>234</sup> on the evidence for efficacy: (1) “conventional” or traditional which is two adequate and well-controlled trials; (2) evidence consistent with some formal FDA system for exercising discretion or “administrative flexibility”; or (3) evidence that is case-by-case (this is neither conventional nor administrative flexibility; orphan drugs sometimes get this exclusion).

I classified a discussion on PMS as “PMS discussion in the context of approval” if a postmarketing study was discussed in the following contexts: (1) pre-approval vs. post-approval study; (2) having postmarketing studies is comforting; (3) postmarketing studies as a condition for

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<sup>234</sup> (1) 1 adequate and well-controlled study with “confirmatory evidence”; (2) 1 study with very persuasive study and where a second study is not feasible; or (3) Accelerated approvals.

approval; and (4) if approved, postmarketing studies should be done. For more details on variables and coding rules, see Table 3-6 in Appendix I.

***Uncertainties, PMR/PMCs, and approval (FDA behavior)***

We can further examine how likely drug applications with discussion on postmarketing studies would actually be approved by the FDA. Diverse factors affect FDA's approval decisions and the FDA does not always concur with its advisory committees. But, the likelihood of approval of drug applications with PMS discussion and ones without PMS discussion should reflect the theory that the postmarketing study options affect the approval process. We expect to observe that drug applications with discussion on PMR/PMCs in the context of approval are more likely to be approved compared to ones without such discussion among drugs with weak pre-approval evidence. And we also want to test whether such relationship exists to a greater extent in Period 2 than in Period 1 because the pressure to approve drugs faster has been increasing as we discussed in Section 3.3.2.

Then, we can look at how many approvals had postmarketing studies. We suppose that drugs with more uncertainty are more likely to have approvals with postmarketing studies. Also, when the committees discuss PMR/PMCs, those drugs with such discussions are more likely to have postmarketing studies when approved compared to the drugs without such discussions. Here, more ideal approach is to look at a relationship between actual number of PMR/PMCs and approval, but PMR/PMC data is not available for Period 1. Thus, we focus on discussions on PMR/PMCs in the context of approval instead of actual PMR/PMCs when looking at both period 1 and period 2. And, we examine actual PM/RPMCs for drug approvals in period 2.

### ***Orphan drugs***

In addition, some interviewees identified a lack of therapy alternatives, rare disease, and narrow target population as important factors to consider when recommending approval for drugs (see Section 3.4.3) with the PMR/PMC options. Orphan drugs particularly fit this type. An FDA staff in a Gastrointestinal committee meeting in 1986 talked about approving orphan drugs: “I think the standards are the same; standards of safety and effectiveness are the same. But there is a willingness to go a little further in looking at kinds of data that would probably not be sufficient for a new antihypertensive agent. And it is a matter of judgment about how far to go.”

Whether the effect of the availability of postmarketing study options on approval process is mostly limited to such drugs is a relevant question. Does the option of postmarketing studies affect approval process for drugs without alternatives or orphan drugs? We also examine whether there were changes in the effect of postmarketing studies on orphan drug approval from the 1980s to the 2010s.

In attempt to answer these questions, albeit indirectly, we can use the orphan drug status at the time of application. Discussion on postmarketing studies in the context of approval is expected to be associated with more positive votes in orphan drugs than in non-orphan drugs: The difference between the percentage of “yes” votes for recommending approval when postmarketing studies were discussed in relation to approval and the percentage of “yes” votes without such discussion is larger in orphan drugs than in non-orphans. We can also test whether such difference is larger in Period 2 than in Period 1.

### **Findings**

### ***Qualitative assessment on the role of PMS in addressing uncertainty issues***

Table 3-18 shows drug approvals by whether postmarketing studies are mandatory or discretionary in Period 2. Mandatory postmarketing studies include accelerated approvals (confirmatory trials) and animal efficacy approvals (field studies in humans). Drugs that are subject to discretionary PMS are non-accelerated and non-animal approvals.

Among the drugs with mandatory PMS, 82% won approval while only 51% of drugs that are subject to discretionary PMS did when first submitted. Including the cases where drugs were approved after resubmission, 91% of drugs with mandatory PMS were approved compared to 63% of drugs without mandatory PMS. And, only half of drugs without mandatory PMS had PMR/PMCs other than PREA studies. This may tell us that drugs approved only with PMS are more likely to be approved than drugs with discretionary PMS, although approval decision is made through complex decision-making process with various observable and unobservable factors (i.e. drugs for serious/life-threatening conditions are more likely to be approved).

**Table R-14. FDA's drug approval decision, by PMS mandatory or discretionary, Period 2**

	PMS-discretionary	PMS-mandatory	Total
Approved	18 (51%)	9 (82%)	27
<i>Approved with PMS</i>	14	9	
<i>Approved with FDAAA</i>	8		
<i>Approved with PREA only</i>	5		
<i>Approved with PREA+PMC only</i>	1		
<i>Approved with AA or animal only</i>		2	
Rejected, but approved later	4	1	5
Not approved	13	1	14
Total	35	11	46

Notes:

1. PMS-mandatory drugs include accelerated approvals and animal efficacy approvals. Therefore, all PMS-mandatory drugs have confirmatory trial and animal rule study requirements. There are two animal efficacy approvals. All accelerated approvals and animal efficacy approvals didn't have PREA studies.
2. PMS-discretionary drugs are non-accelerated approvals and non-animal efficacy approvals. Among 35 PMS-discretionary drugs, approval rates vary: (1) 53% in new drugs and 40% in supplements; (2) oncology drugs 38%, cardiovascular and renal drugs 40%, gastrointestinal drugs 100%, and antimicrobials 67%.

Now, we can look at the drugs that were rejected and approved to examine whether PMR/PMCs played any role in addressing issues with uncertainty. First, let us look at drugs whose applications were rejected when first submitted but approved later with additional information in Period 2<sup>235</sup>. In the sample, there are 5 drugs whose approvals were rejected when first submitted (4 PMS-discretionary and 1 PMS-mandatory in Table 3-18). Appendix P shows details on FDA's rationale for rejection and advisory committee discussion, and FDA's final decisions on approval and PMR/PMCs.

Three out of five drugs had approvals without PMR/PMCs when resubmitted. The rationales for rejection provided by FDA include (1) unfavorable benefit risk ratio for the proposed indication, (2) doubtful clinical relevance of primary endpoint, and (3) not substantial effect with lack of mortality data. For these issues, PMR/PMCs did not have roles in reducing uncertainties or resolving issues. After resubmission, Tobi Podhaler (NDA #201688, Antimicrobial) was approved with 3 FDAAA safety PMRs and 1 PMC, and FDAAA safety studies partially address the concerns shared by the committee. But, the reason FDA rejected the first application was facility inspection problem rather than the benefit-risk profile of the drug. In this case, I found no to little role of PMS in reducing uncertainties.

The only case I found some role of PMS in addressing uncertainties was Northera (NDA #203202, cardiovascular) with accelerated approval. When first submitted, FDA rejected approval because only 1 out of 3 trials showed positive results and the durability of effect was uncertain. The applicant submitted results from a new randomized trial for a slightly different indication.

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<sup>235</sup> Approval package is usually not available for the drugs approved in Period 1.

FDA accepted it, but the durability of effect was still uncertain. A confirmatory trial was required to prove the durability of effect.

Next, let us turn to the successful cases (see Appendix O for details): a total of 27 drugs were approved when first submitted in Period 2 (18 PMS-discretionary and 9 PMS-mandatory). Out of 27, 10 drugs (37%) had no applicable PMR/PMCs: 4 drugs were approved without PMR/PMCs, 5 drugs had PREA studies only<sup>236</sup>, and 1 drug had an animal rule<sup>237</sup> study only.

Among 17 drugs with applicable PMR/PMCs (AA confirmatory trials, FDAAA safety studies, and PMCs), 7 drugs were approved with accelerated approval and FDA established relevant PMR/PMCs that address concerns and uncertainties related to safety (5), dose (1), and efficacy (1) for these 7 accelerated approvals. One drug (Raxibacumab) was animal efficacy approval with a PMC on immunogenicity in addition to animal rule study. The issue of immunogenicity was raised during the meeting.

Out of 10 non-accelerated approvals with PMR/PMCs, 8 drugs had PMR/PMCs that played some role in addressing uncertainties: safety issues (4), drug resistance (2), immunogenicity (1), and pregnancy/male hormonal issues (1). For Cresemba (NDA #207500/207501, antimicrobial)<sup>238</sup> and Marqibo (NDA #202497, oncologic)<sup>239</sup>, I found unclear or limited role of PMS in addressing major uncertainties the committee discussed.

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<sup>236</sup> It is very unlikely that the option of PREA studies affects approval decision and that PREA studies reduce uncertainties/concerns raised by the committee.

<sup>237</sup> By law, drugs approved with animal rule are subject to a PMR for a field study on humans. The option of animal rule studies is very unlikely to affect approval decision and to have role in reducing uncertainties.

<sup>238</sup> It had 3 FDAAA studies (5-year susceptibility study, two carcinogenicity studies) and 1 PMC (patient registry). But, the PMRs are not relevant to the major concerns raised by the AC. Although the PMC might be relevant, it is not clear if the PMC address the major concerns discussed by the AC.

<sup>239</sup> PMRs didn't address the major concerns raised by the committee. A PMC addresses concerns shared by FDA reviewers – safety issues related to manufacturing and preparation.

We can further examine PMS-mandatory drugs where approvals always come with PMRs and these drugs are either accelerated approvals or animal efficacy approvals (See Appendix Q for further details). There are 9 accelerated approvals and 2 animal efficacy approvals in Period 2 in the sample (Table 3-19). There were two drugs that were denied when first submitted. Rociletinib had low response rate and the committee recommended the FDA to wait until the phase 3 trial results due to high uncertainty (lack of data, variable PK, lack of power, etc.)<sup>240</sup> The other drug is Northera. Northera was rejected when first submitted due to uncertain trial results and durability of effect. When resubmitted, the former issue was resolved but durability of effect was still the problem. Thus, FDA required the sponsor to study the durability of effect in its AA requirement.

**Table R-15. PMS-mandatory drugs (AA and Animal), Period 2**

Drug	Approval	Votes	Types	Division	Modified Indication	BBW	PMS role
Rociletinib	Rejected	8%	First in class, AA	Oncologic	-	-	-
Northera	Rejected, but approved later	first 58%, later 94%	First in class, AA	Cardiovascular	Yes	Yes	Yes
Lynparza	Approved	15%	AA	Oncology	Yes	No	Yes
Farydak**	Approved	29%	AA	Oncology	Yes	Yes	Yes
Perjeta	Approved	93%	Suppl., AA	Oncology	No	Yes	Yes
Marqibo	Approved	54%	AA	Oncology	No	Yes	Limited
Kyprolis	Approved	92%	AA	Oncology	Yes	No	Yes
Ocaliva	Approved	100%	First in class, AA	Gastrointestinal	No	No	Yes
Levaquin	Approved	100%	Suppl., Animal	Antimicrobial	No	No*	No
Raxibacumab	Approved	100%	Animal	Antimicrobial	No	No	Yes
Sirturo	Approved	No voting	First in class, AA	Antimicrobial	No	Yes	Yes

Notes: \* already had black box warning \*\* had REMS as well

See Appendix Q for further details

In two denied cases, we observe that FDA reject applications even when PMRs are guaranteed if the study results have high uncertainty or low effect. In other cases, even when the

<sup>240</sup> The sponsor stopped all on-going investigations and withdrew its application. The sponsor was also facing federal probe on data for the drug—\$20M settlement with SEC was offered by the sponsor in August 2, 2018.

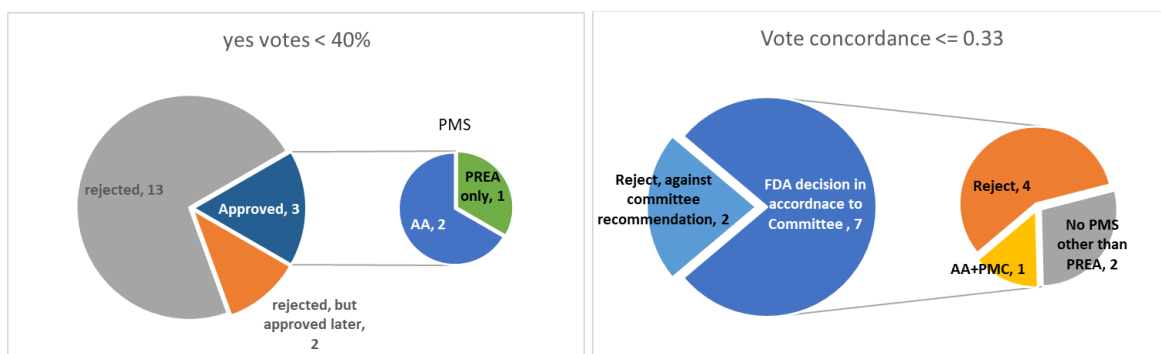
committees recommend non-approval, FDA approved the drugs and PMR/PMCs address some of the concerns and uncertainties shared by the committees.

***Use of PMR/PMCs when there was disagreement on approval decision***

Then, how frequently does the FDA use PMR/PMCs to manage uncertainty when it approves a drug that the advisory committees didn't recommend? Figure 3-9 shows the number of drugs by FDA's decision and how many of the drugs approved had PMS when the majority of committee voted no and votes were split.

When the percentage of yes votes was low (0%-40%), the agency approved 3 drugs out of 18 drugs (17%). Two of them were accelerated approvals and the other one didn't have relevant PMR/PMCs other than PREA studies. When we look at the cases where the decision was debatable (vote concordance  $\leq 0.33$ ; see notes in Figure 3-9), FDA decision was in accordance to the committee decisions in 7 out of 9 drugs. In two cases, FDA went against the committee recommendation by rejecting those applications. There was only one drug (Marqibo, oncologic) with PMR/PMCs that are relevant to the issues and concerns discussed among the committee and FDA before making approval decision.





**Figure R-7. FDA's decision on approval and PMS, by the committee votes, Period 2**

Notes:

1. The sample includes the drugs with voting in Period 2. On the left figure, 18 drugs had yes votes lower than 40%. On the figure right, 9 drugs had less than 0.33 of vote concordance (% yes votes range from 36% - 63%). Vote concordance = Absolute value of difference between yes and no / sum of yes and no votes. Absent votes were not counted. If the votes were unanimous, the vote concordance is 1. Vote concordance lower than 0.33 is considered the votes were split.
2. On the right figure, "reject" includes drugs rejected but approved later. The only case where PMS did play some role in addressing concerns about drug approval was Marqibo (oncologic, AA) that had 7 yes, 4 no, and 2 abstain.
3. PMCs that are not subject to report under section 506(B) are not included. These PMCs are related to manufacturing and chemical controls.

Let us look at individual cases on the left Figure 3-9. One of the drugs that had low yes votes but was approved is Lynparza (oncologic). The drug earned 15% yes votes (they recommended FDA for further data) due to the lack of an overall survival benefit for maintenance therapy; the unreliability of the results due to loss of randomization and small sample size; the toxicity of therapy and risk of MDS/AML<sup>241</sup> for patients not otherwise undergoing treatment; and the potential to hinder accrual to confirmatory study. When approved, FDA modified the proposed indication. The agency justified the response rate of 34% is better than what would be expected of any available therapy and the surrogate endpoint is likely to predict the clinical benefit. The agency also argued that the serious risk of MDS/AML is acceptable because of poor availability of other therapies. And FDA required 2 confirmatory trials and 3 FDAAA studies and some of them address

<sup>241</sup> myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)

a different endpoint (overall survival) as well as the risk of leukemia. The other drug is Farydak (oncologic)—quite similar case to Lynparza. FDA approved this drug with accelerated approval for a modified indication. And it required two confirmatory trials (a phase 2 and phase 3 trial).

On the other hand, there was a case where PMS issue rather delayed approval. *Phenylephrine hydrochloride* (cardiovascular) had been in the market for long time without FDA approval and the agency encouraged the application for IV form. The committee, on the other than, didn't recommend approval (20% yes votes) and several members felt that the proposed indication was too broad. The committee also recognized the need for additional longer-term use and criteria, adequately characterized safety profile, and collecting data in general anesthesia. The FDA review team didn't think PMS was necessary and decided to approve the drug with slightly different indication.<sup>242</sup> But there was an internal disagreement on PREA requirements.<sup>243</sup> This delayed approval and finally this drug was approved when the sponsor proposed acceptable timeframe for PREA study.

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<sup>242</sup> This application proposed for “to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension.” Prior to the vote, the committee expressed consensus for approval for an indication in neuraxial anesthesia and peri-operative hypotension. Those who voted “no” noted that the indication was too broad. It was commented that in order to gain approval in a broader indication this would require data similar to a non-inferiority study against other agent. FDA approved this drug for “increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.”

<sup>243</sup> In Complete Response Letter on 11/9/2012, an FDA reviewer in Division of Cardiovascular and Renal Products wrote “I previously (memo of 19 October) concluded that this application was approvable. An initial consensus was reached to waive requirements under PREA, and agreement with PERC (Pediatric Review Committee) was obtained. Subsequently, DAAAP (Division of Anesthesia, Analgesia, and Addiction Products) altered its opinion regarding the need for data in children age 12 and up, and since the responsibility for this application devolves to them upon approval, it seemed appropriate to honor their request for a PREA study. Time did not permit negotiation of the details or timing with the sponsor, so a Complete Response letter will now be issued, naming the PMR as the sole barrier to approval.” On 12/20/2012 CRL, “This application was previously given a Complete Response (memo of 9 November 2012) with the only issue being negotiation of the timeframe for completing a PMR relating to a study in children. The sponsor has proposed a timeframe that is acceptable to DCaRP (Division of Cardiovascular and Renal Products), DAAAP, and PeRC.”

**Table R-16. Drugs approved by FDA, amidst disagreement, in Period 2**

Drug	Division	AC votes	AA	PMS other than PREA	Modified indication	BBW
Lynparza	Oncologic	Low yes votes	Accelerated	Yes	Yes	No
Farydak	Oncologic	Low yes votes	Accelerated	Yes, also REMS	Yes	Yes
Phenylephrine hydrochloride	Cardiovascular	Low yes votes	Traditional	No	Yes	No
Portrazza	Oncologic	Low vote concordance	Traditional	No	No	Yes
Marquibo	Oncologic	Low vote concordance	Accelerated	Yes	No	Yes
Zinplava	Antimicrobial	Low vote concordance	Traditional	No	Yes	No

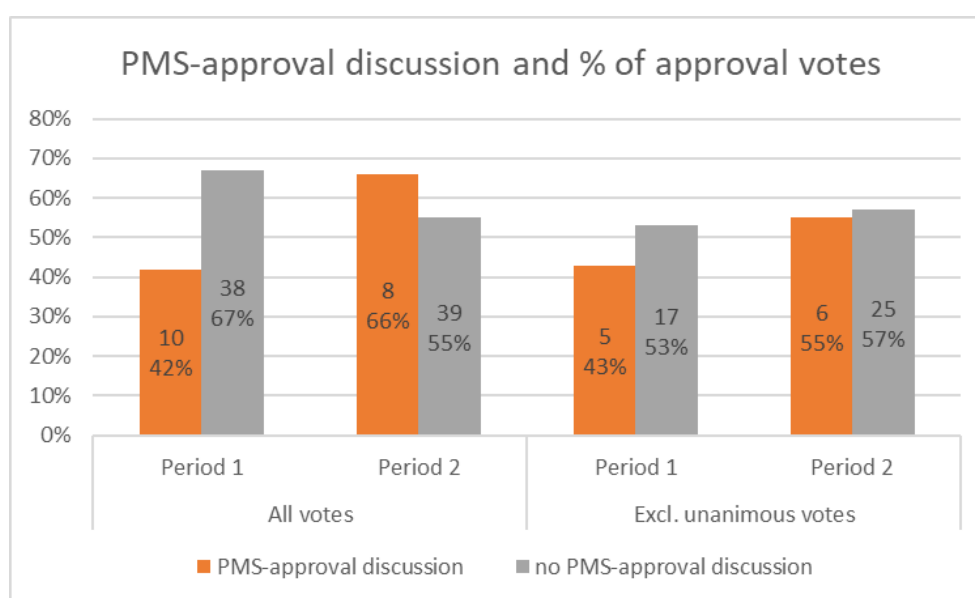
Sometimes, there are disagreements between FDA and advisory committees and among the committee members. When there were disagreements about drug approvals in Period 2 (Table 3-20), FDA is more likely to approve if accelerated approval. And, half of time (2 on the left Figure 3-9 and 1 on the right Figure 3-9), the agency required or negotiated PMR/PMCs that could address potential risks and uncertainties—they were all AA drugs.

Furthermore, FDA has approved drugs, amidst disagreements, for modified indications (4 out of 6) to concur with opinions and concerns raised by AC. Also, mostly, these cases are observed in oncologic drugs (4 out of 6); 1 antimicrobial drug and 1 cardiovascular drug were observed. In sum, FDA uses various tools—labeling with black box warnings, modifying the proposed indications, and PMR/PMCs. The role of PMR/PMCs in reducing potential uncertainties is more likely to be observed in accelerated approvals.

#### ***PMR/PMC discussion and committee votes***

Next, we can examine the voting results when postmarketing studies were discussed. Here, we assume that the cases brought to FDA advisory committees present more uncertainty. We expect that the availability of postmarketing study options at the time of approval (represented by the presence of PMS discussion in the context of approval) increases the likelihood of “yes” votes.

On average, higher number of members voted for approval in Period 1 (62%) than Period 2 (57%). Figure 3-10 exhibits the average percentage of votes for approval when postmarketing studies were discussed in the approval context. When they discussed postmarketing studies in the context of approval, the percentage of votes for approval in Period 2 is 66% which is higher than 42% in Period 1. Without PMS-approval discussions, the percentage decreased from 67% in Period 1 to 55% in Period 2.



**Figure R-8. Average percentage of for approval by PMS-approval discussion**

Note: accelerated approvals are excluded from the analysis. The unit of analysis is meeting agenda.

In Figure 3-10, the percentage of votes for approval, excluding unanimous cases, is shown in the second column section. The rationale for excluding unanimous cases is that one can assume that unanimous cases are rather “easy” ones making little room for postmarketing studies to work in approval decisions. Excluding unanimous votes, the average percentage of members who voted for approval was higher in Period 2 (57%) than Period 1 (51%). When the committees discussed

PMS in relation to approval, the percentage of approval votes increased to 55% in Period 2 from 43% in Period 1.

When we observe higher percentage of “yes” votes and unanimous “yes” votes in cases where committees discussed postmarketing studies in Period 2, we could consider three possible scenarios: (1) the case was perceived by committees positively (without PMS discussion) and PMS discussion reinforced the positive thoughts among the committee members and brought more yeses; (2) the case tied for approval without PMS discussion and PMS discussion brought more yes votes; and (3) the case was perceived by committees negatively but PMS discussion had some committee members (who originally thought negatively about the case) change their mind to yes.

Now, we can take a look at the vote concordance (the ratio of the difference between “yes” votes and “no” votes to the total number of votes). Higher vote concordance means that committee members agree with each other to a greater extent. For the first two scenarios, we should observe higher vote concordance when PMS was discussed. The only case where we may observe lower vote concordance is the third scenario where more committee members had negative views on approval.

Table 3-10 in Appendix I presents the vote concordance when postmarketing studies were discussed, discussed extensively, and discussed in the context of approval. One noticeable pattern observed in vote concordance for Period 2 is that if postmarketing is discussed, vote concordance remains same or lower. This means that committee members agree to each other to a lesser extent when postmarketing studies are discussed. This finding weakens the first two scenarios presented above and suggests that having the PMS options is more likely to change “no” votes to “yes” votes when it is a “less likely approvable” case. Therefore, the higher percentage of unanimous yes votes is less likely to suggest that PMS discussion brought unanimous votes. PMS discussion didn’t play

a large role in “more approvable” cases. Rather, PMS discussion may have larger influence on approval when the case is difficult to be approved.

### ***PMS discussion and approval***

Now, how likely would drug applications with discussion on postmarketing studies be approved by the FDA? Again, the likelihood of approval is determined by various factors and drug profiles, but we may observe higher rate of approval in drug applications that had PMS discussion in the context of approval. Also, we might expect that such relationship exists, to a greater extent, in Period 2 than in Period 1.

Table 3-21 presents FDA’s approval decisions when the discussion was in the context of approval. Average FDA approval rate was higher in Period 1: more drugs were approved in Period 1 (89%) compared to Period 2 (63%) after a committee meeting. Note that time to approval was not considered; more time is allowed for drugs in Period 1 and half of the drugs was approved long after the meeting, but drug approval is faster today than 30 years ago. When the committees discussed PMS in relation to approval, more drug applications were approved in Period 2 (75%) and less often drugs were approved in Period 1 (83%). This suggests that PMS discussion and PMS discussion in the context of approval may be associated with approval decision in Period 2 rather than Period 1.

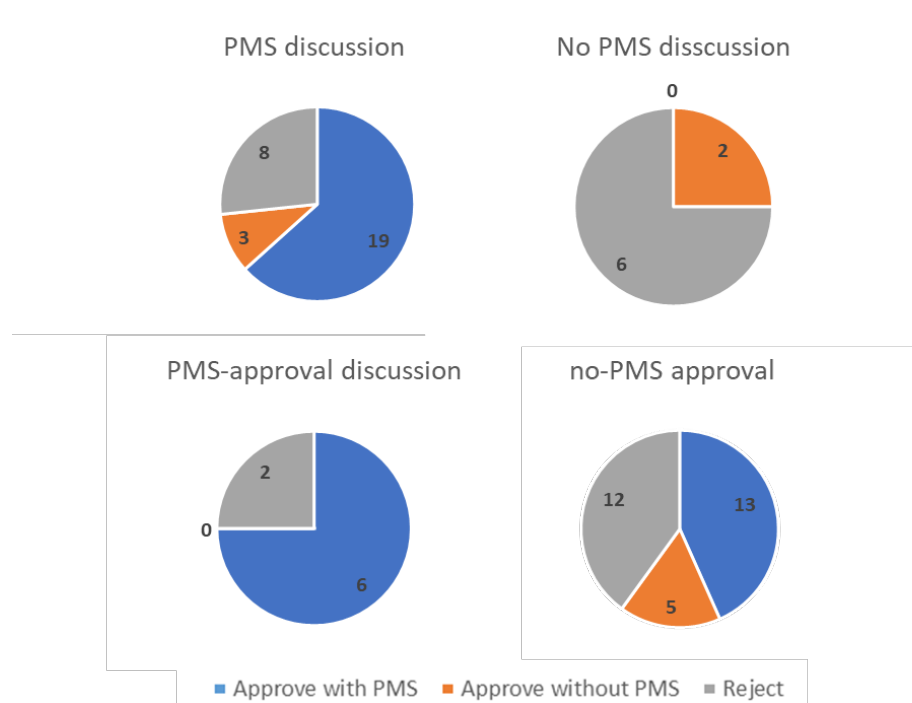
**Table R-17. Approval decisions when the discussion was in the context of approval**

Number of advisory committee meetings with approval decision	Total		PMS-approval discussion	
	Period 1	Period 2	Period 1	Period 2
Approvals	40 (89%)	24 <sup>2</sup> (63%)	10 (83%)	<b>6 (75%)</b>
No approvals	5	14	2	2
Total	45 <sup>1</sup>	38	12	8

Notes: accelerated approvals are excluded

1. In period 1, information on drug approval is not available for 1 drug.
2. In period 2, 38 committee agendas (applications) had FDA approvals after meeting. Among them, 32 were with actual PMR/PMCs and 6 were without those postmarketing studies.

Note that, in Table 3-21, the data count drug approvals with PMS discussion not drug approvals with actual PMR/PMCs. PMR/PMC data are not available for drug approvals in Period 1. In Period 2, 84% (32 out of 38) of drug applications referred to advisory committees were approved with PMR/PMC. Figure 3-11 presents more detailed FDA's final decisions (approval with postmarketing studies, approval without postmarketing studies, and reject approval) by the presence of discussion on postmarketing studies and discussion on postmarketing studies in the context of approval at the committee meetings, during 2012-2016.



**Figure R-9. FDA final decision by PMS discussion and PMS-approval discussion, Period 2**

Note: accelerated approvals are excluded. The unit is drug approval.

In Figure 3-11, we observe a significant increase in approvals with PMR/PMCs when the committees discussed PMR/PMCs and discussed them in the context of approval. When postmarketing studies were discussed in the context of approval, there is no drug approved without PMR/PMCs. Also, when postmarketing studies was discussed, we observe a decrease in approvals without PMR/PMCs.

### ***The level of evidence requirements as level of uncertainty and approval process***

To test whether PMR/PMC discussion is associated with higher yes votes and approval rate by the level of uncertainties, I coded the level of efficacy evidence as explained in Section 3.3.2. Among indications approved during 2012-2016, 23% of approvals had conventional efficacy evidence standard and 60% of approvals had administrative flexibility. This is similar to the effectiveness evidence standards used for orphan drug approvals: 30% (8 out of 27) during 2010-2014 and 33% (45 out of 135) during 1983-2010 had conventional efficacy evidence standard (Sasinowski, 2012; Sasinowski et al., 2014). These percentages of approvals with conventional standard are slightly higher than the one in this study because Sasinowski's two studies include new drugs only.

Table 3-22 provides the difference in the percentage of yes votes and FDA approval rate between drugs with PMS discussion in the context of approval and drugs without such discussion. Compared to conventional efficacy evidence, drug applications that enjoyed administrative flexibility had higher percentage of votes for approval and approval rate both in drugs when PMS was discussed in relation to approval. But, when such discussion did not take place, the percentage of approval votes for drugs with administrative flexibility was lower than the drugs with conventional efficacy evidence.



**Table R-18. Efficacy evidence<sup>244</sup> and voting/approval results when postmarketing studies were discussed in relation to approval, for Period 2 only<sup>245</sup>**

Evidence of efficacy	PMS-approval discussed			PMS-approval not discussed		
	No.	% votes for approval	Approved by FDA	No.	% votes for approval	Approved by FDA
Conventional	3	72%	2	7	94%	7
Administrative flexibility	<b>3</b>	<b>85%</b>	<b>3</b>	13	71%	11
Case-by-case flexibility	1	20%	1	1	100%	1
N/A	1	40%	-	21	27%	7

Data Source (partially): Sasinowski (2012) and Sasinowski et al. (2014).

1. Accelerated approvals are excluded
2. N/A: information not available or cannot be judged

When comparing drugs with PMS-approval discussion and drugs without PMS-approval discussion, we observe higher average percentage of votes for approval in the former (85%) than in the latter group (71%) with administrative flexibility. For those with conventional efficacy evidence, we find lower average percentage of votes for approval in the former (72%) than in the latter group (94%). Sample size is too small to draw a definitive inference.

But, this table does not nullify the hypothesis. Drugs with conventional efficacy evidence represent drugs with less uncertainty and the percentage of “yes” votes was lower when committees discussed postmarketing studies in relation to approval. Drugs with administrative flexibility represent drugs with more uncertainty. And, the percentage of “yes” votes was higher when committees discussed postmarketing studies in relation to approval.

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<sup>244</sup> I adopted Sasinowski (2012) and Sasinowski et al. (2014) classification methods. I also imported their data when applicable. For most part, I looked at drug approval package (clinical and statistical-efficacy review section, especially) where the FDA reviewers evaluate key clinical trials supporting the approval.

<sup>245</sup> Drug approval package was not available for most of drugs approved during 1985-1988. Among 3 drug-approvals with available data, one had conventional efficacy evidence (2 trials), another one had administrative flexibility (1 confirmatory trial), and I couldn't determine the level of efficacy evidence for the last one.

### ***Orphan drugs***

Lastly, as stated in the methods and theoretical framework Section in 3.3.2, we can examine whether the effect of the postmarketing study options on approval process is limited to certain drugs or widespread across all drug types.

Table 3-23 shows that both in Period 1 and Period 2, with PMS discussion in the context of approval, the percentage of votes for approval increased in orphan drugs. In Period 2, we see a larger increase (from 61% to 73%) compared to Period 1 (from 73% to 79%). For non-orphan drugs, in Period 1, the percentage of votes for approval when postmarketing studies were discussed is lower than the average percentage of approval votes without such discussion. On the contrary, in Period 2, the percentage of “yes” votes is higher when the committees discuss PMR/PMCs for non-orphan drugs. But, the percentage difference in non-orphan drugs is smaller than in orphan drugs.

**Table R-19. Orphan and Non-orphan drug approvals**

		Period 1		Period 2	
		% yes votes <sup>3</sup>	FDA Approval <sup>4</sup>	% yes votes <sup>3</sup>	FDA Approval <sup>2</sup>
Orphan	Total	74% (8)	7/7 (100%)	63% (24)	8/13 (62%)
	PMS-approval discussion <sup>1</sup>	79% (2)	2/2 (100%)	73% (4)	3/4 (75%)
	Without PMS-approval discussion	73% (6)	5/5 (100%)	61% (20)	5/9 (56%)
Non-orphan	Total	59% (48)	33/39 (85%)	55% (35)	16/25 (64%)
	PMS-approval discussion <sup>2</sup>	32% (10)	8/10 (80%)	59% (4)	3/4 (75%)
	Without PMS-approval discussion	66% (38)	25/29 (86%)	54% (31)	13/21 (62%)

Notes:

1. The cases where the committees discussed postmarketing studies in relation to approval
2. Approval percentage: the percentage of approved (by the FDA) drug applications discussed in the meetings under each category. The unit is drug approval.
3. Vote % approval: the average percentage of votes for approval in the committee meetings under each category. The unit is indication (meeting agenda)

*Summary findings from advisory committee meetings and FDA approval decision*

- Drugs are more likely to be approved when PMS are mandatory.
- PMS discussion didn't play a large role in "more approvable" cases. Rather, PMS discussion may have larger influence on approval when the case is difficult to be approved.
- PMS discussion and PMS discussion in the context of approval may be associated with approval decision in Period 2 rather than Period 1. And, drugs are more likely to be approved with PMS when the committees discussed PMR/PMCs and discussed them in the context of approval.
- When PMS was established, the PMS is more likely to address the concerns with uncertainties discussed before approval (80% of time).
- Issues of unfavorable benefit-risk profile, low effectiveness, doubtful clinical relevance, effect size, and disagreement about endpoints are more likely to result in rejection (rather than approval with PMS)—PMS perhaps do not play large role in approval.
- Role of PMR/PMCs in reducing potential uncertainties is more evident in accelerated approvals. And, AA requirements are aimed to not only confirm clinical benefit of the drug but also address the issues raised before approval—i.e. Northera
- FDA employs various ways to deal with uncertainties—PMR/PMCs, labeling such as black box warning, and/or modified indication. It is not rare that FDA approves drugs with narrower indication than originally suggested to cope with the potential uncertainties identified.
- When PMS-approval discussion takes place, orphan drugs are more likely to be approved compared to non-orphan drugs.