Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved Between 2009 and 2012: a Cross-Sectional Evaluation

Journal:	*BMJ*
Manuscript ID	BMJ.2018.043625
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	07-Feb-2018
Complete List of Authors:	Wallach, Joshua; Yale University, Collaboration for Research Integrity and Transparency; Yale University Center for Outcomes Research and Evaluation, Egilman, Alexander; Yale University Yale Law School, Collaboration for Research Integrity and Transparency Dhruva, Sanket; Yale University, Robert Wood Johnson Foundation Clinical Scholars Program McCarthy, Margaret; Yale Law School, Collaboration for Research Integrity and Transparency Miller, Jennifer; New York Langone Medical Center, Population Health; Harvard University, Edmond J. Safra Center for Ethics woloshin, steven; VA Medical Center / Dartmouth medical school, Schwartz, Lisa; Dartmouth College Geisel School of Medicine, The Dartmouth Institute for Health Policy and Clinical Practice; Dartmouth Institute for Health Policy and Clinical Practice Ross, Joseph; Yale University School of Medicine, Internal Medicine
Keywords:	Postmarketing requirements, FDA, Lifecycle evaluation

Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved Between 2009 and 2012: a Cross-Sectional Evaluation

Joshua D Wallach; Alexander C Egilman; Sanket S Dhruva, Margaret E McCarthy; Jennifer E Miller; Steven Woloshin; Lisa M Schwartz; Joseph S Ross

Joshua D Wallach, Postdoctoral Research Fellow
Center for Outcomes Research and Evaluation (CORE), Yale-New Haven Hospital and Collaboration for Research Integrity and Transparency (CRIT), Yale Law School, New Haven CT, USA

Alexander C Egilman, Research Associate
Center for Outcomes Research and Evaluation (CORE), Yale-New Haven Hospital and Collaboration for Research Integrity and Transparency (CRIT), Yale Law School, New Haven CT, USA

Sanket S Dhruva, Postdoctoral Research Fellow
Robert Wood Johnson Foundation Clinical Scholars Program; Veterans Affairs Connecticut Healthcare System, New Haven CT, USA

Margaret E McCarthy, Executive Director
Collaboration for Research Integrity and Transparency (CRIT), Yale Law School, New Haven CT, USA

Jennifer E Miller, Assistant Professor
Division of Medical Ethics, Department of Population Health, NYU School of Medicine and Bioethics International, New York NY, USA

Steven Woloshin, Professor of Medicine
Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon NH, USA

Lisa M Schwartz, Professor of Medicine
Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon NH, USA

Joseph S Ross, Associate Professor of Medicine and Public Health
Section of General Medicine and the National Clinician Scholars Program, Department of Internal Medicine, Yale School of Medicine; Department of Health Policy and Management, Yale School of Public Health; and Center for Outcomes Research and Evaluation, Yale-New Haven Health System, New Haven CT, USA

Corresponding author:
Joshua D Wallach, MS, PhD
Collaboration for Research Integrity and Transparency (CRIT), Yale Law School; and Center for Outcomes Research and Evaluation, Yale-New Haven Health System, New Haven, CT, USA
Email: joshua.wallach@yale.edu

Key words: Postmarketing requirements; FDA; lifecycle evaluation
Word count: 4383
Figures/Tables: 5
References: 29
Appendix: 2

ABSTRACT

Objective To characterize the postmarketing requirements for new drugs and biologics approved by the US Food and Drug Administration (FDA), and to examine the rates and timeliness of registration and results reporting on ClinicalTrials.gov and publication of required prospective cohort studies, registries, and clinical trials in peer-reviewed journals.

Design Cross-sectional analysis.

Setting Postmarketing requirements for all new drugs and biologics approved by the FDA between January 1, 2009 and December 31, 2012, with follow-up through November 26, 2017.

Main outcome measures Postmarketing requirements and their characteristics known at the time of FDA approval, including FDA authority, study design, and study characteristics. Rates and timeliness of registration and results reporting on ClinicalTrials.gov and publication in peer-review journals of prospective cohort studies, registries, and clinical trials, as determined from PubMed and Scopus searches.

Results Between 2009 and 2012, the FDA approved 97 new drugs and biologics for 106 indications with at least one postmarketing requirement at the time of first approval, for a total of 437 postmarketing requirements. Postmarket study descriptions were often short (median word count of 44 [interquartile range (IQR), 29-71]) and there was not enough information to determine the progress of nearly one-third (131 of 437 [30.0%]). Half (220 [50.3%]) of the 437 postmarketing requirements were for new animal or 'other' studies, including pharmacokinetic and in vitro/in vivo studies, whereas nearly one-third (134 [30.7%]) were for prospective cohort studies, registries, and clinical trials. Among the 110 clinical trials, there was not enough information to establish use of randomization, comparator type, allocation, and outcome for 38 (34.5%), 44 (40.0%), 62 (56.4%) and 66 (60.0%), respectively. Just over three-fourths (n=102, 76.1%) of the required prospective cohort studies, registries, and clinical trials were registered on ClinicalTrials.gov. Among the 50 registered and completed studies, 36 (72.0%) had reported results on ClinicalTrials.gov. Among the 65 completed studies, regardless of ClinicalTrials.gov registration, 36

(55.4%) were published in the peer-reviewed literature. Among the 47 studies that either reported results or were published, the median time from FDA approval to reported results or publication was 47 (IQR, 32-67) months. Two-thirds (32 of 47 [69.1%)] of studies did not report results publicly by the time of their original FDA report submission deadline.

Conclusions

Postmarketing requirements for new drugs and biologics were often briefly described and did not contain enough information to characterize the required study designs. While three-fourths of postmarketing requirements for prospective cohort studies, registries, and clinical trials were registered on ClinicalTrials.gov, and nearly three-fourths of completed studies reported results or were published, there remain opportunities to improve dissemination of these required studies to inform clinical care.

What is already known on this subject

- FDA can require drug sponsors to conduct studies after approval to answer important questions about the safety and efficacy of new drugs and biologics (i.e. postmarketing requirements).
- There have been growing concerns about the fulfillment of postmarketing requirements, and when fulfilled, the rigor of the evidence generated.
- One-third of "fulfilled" required postmarket clinical trials are not published in either the scientific literature or reported on ClinicalTrials.gov**.**

What this study adds

- Many postmarketing requirements issued by FDA at the time of approval were only briefly described and often did not contain enough public information to understand the purpose of the requirement or characterize the study designs.
- Among required prospective cohort studies, registries, and clinical trials, approximately three-fourths were registered on ClinicalTrials.gov, whereas among all registered or unregistered studies for which results reporting or publication would be expected, nearly three-fourths had done so.
- Among required prospective cohort studies, registries, and clinical trials that either reported results or were published, the median time from FDA approval to reporting or publication was approximately 4 years, with two-thirds not reporting results publicly by the time of their original FDA report submission deadline.

INTRODUCTION

In the United States, the Food and Drug Administration (FDA) requires all new drugs and biologics to undergo clinical testing to demonstrate that they are safe and effective. However, over the last decade, FDA has increasingly approved new drugs and biologics on the basis of less robust evidence, including shorter, smaller, and fewer trials.[1] This shift corresponds with FDA's adoption of a "lifecycle evaluation", which emphasizes the importance of continued evaluation and monitoring of safety and effectiveness in the postmarket period.[2-5] Reflecting this emphasis, FDA can use four separate authorities to require drug sponsors to conduct studies after approval to answer important questions about the benefits, harms, and optimal uses of new drugs and biologics (i.e. postmarketing requirements, **Box 1**).[6]

Postmarket studies required by FDA can have important public health implications. Their findings can provide new evidence on the safety and efficacy of approved drugs and biologics, which can lead to regulatory actions and help guide decisions made by payers, physicians, and patients.[7] However, over the last few years, there have been growing concerns about the fulfillment of postmarketing requirements.[8-10] For instance, one analysis of all new drugs and biologics granted accelerated approval between 2009 and 2013 found that at a minimum of 3 years of follow-up, only half of the required confirmatory studies were completed.[9] However, postmarket studies required under the Accelerated Approval pathway represent less than 4% of all postmarketing requirements issued by the FDA between 2008 and 2014.[7]

Furthermore, it is not sufficient for postmarket studies to be completed; successful translation of clinical trial evidence into practice requires timely dissemination of their results. A recent internal evaluation by FDA found that over one-third of "fulfilled" postmarket studies were not published in either the scientific literature or on the ClinicalTrials.gov website.[11] However, the authors were able to rely on internal agency information, as opposed to information that is available to the public, and did not examine

the proportion of all clinical study postmarketing requirements that were fulfilled, the rigor of the evidence generated, nor the timeliness of results reporting.

Given the increasing reliance on FDA postmarketing requirements for new drugs and biologics, we sought to characterize them for all new drugs and biologics approved between 2009 and 2012. In particular, we evaluated the different types of required studies under the four separate FDA authorities; the status of these postmarket studies using publicly available data sources; and the study characteristics and rates and timeliness of registration and results reporting on ClinicalTrials.gov and publication in peer-review journals of postmarketing requirements for clinical studies: prospective cohort studies, registries, and clinical trials.

Methods

Study design and sample

We used the publicly available Drugs@FDA database to identify and categorize all new drug and biologic licensing applications for drugs and biologics first approved between January 1, 2009, and December 31, 2012, excluding generic drugs, reformulations, and combination therapies of non-novel therapeutic agents, using a previously described approach.[1,12] We selected 2012 as a cut-off date to allow for at least four years for completion and publication of required postmarket studies. New drugs and biologics were classified by orphan status, using a previously described approach.[1]

FDA approval letters were used to determine the first-approved indication for each new drug and biologic and FDA priority review status (i.e. review required to be completed within 6 instead of 10 months).[13] The Fast Track designation, which provides enhanced communication with FDA during the development process, and the Breakthrough Therapy designation, which was not implemented until 2014, were not assessed in this study.[1] The World Health Organization's Anatomic Therapeutic Classification system was used to categorize each indication.[14] Indications were then grouped into one of six therapeutic areas (cancer; infectious disease; cardiovascular disease and diabetes mellitus; autoimmune, musculoskeletal, and dermatology; neurology and psychiatry; and other).[14]

Identifying Postmarketing Requirements and Postmarketing Requirements Features

One reviewer (JDW) identified all postmarket studies that FDA required (i.e. postmarketing requirements) from the approval letters hyperlinked in the Drugs@FDA database - which include a brief description of the study type and regulatory authority (Accelerated Approval, Pediatric Research Equity Act (PREA), Animal Efficacy Rule, or the Food Drug Administration Amendments Act (FDAAA), **Box 1**). We also recorded the dates that FDA sets for important milestones: final protocol submission, trial completion, and final report submission, when available. We then classified each postmarketing requirement into six study categories (**Box 2**). When only limited information was available, we used strict classification criteria. For example, a one sentence postmarketing requirement for a pharmacokinetic study, without study duration or outcomes, would be classified as a "new animal or 'other' study required", since there may be inconsistent registration and results reporting of pharmacokinetic (PK) and phase 1 trial data on ClinicalTrials.gov.[15] However, a postmarketing requirement evaluating "PK, safety, and efficacy" would be classified as a "new prospective cohort study, registry, or clinical trial". If a ClinicalTrials.gov registration or a corresponding publication had more information, we incorporated that information to improve the fidelity of our categorization.

Using only the information from FDA approval letters hyperlinked in the Drugs@FDA database, we calculated the length of each postmarket study description (word count) and abstracted whether there was information provided about the use of randomization; whether patient allocation was double blind, single blind, open-label, or unclear; whether there was a comparator; whether the comparator was placebo, active control, both, or unclear; and study duration.

Status of Postmarket Studies

The Postmarketing Study and Clinical Trial Requirements and Commitments Database File (available as of October 31, 2017 and downloaded on November 10, 2017), which is publicly accessible through FDA's website and includes descriptions, schedules for completing, and characterizations of the current status of postmarketing requirements,[16] was used to determine the status for each postmarket study. It is updated once per quarter, at the end of January, April, July, and October, based on a FDA review of Annual Status Reports sponsors submit. FDA assigns each postmarketing requirement to one of

seven status categories (**see supplementary appendix box 1**). Because *Fulfilled* and *Released* requirements are only displayed on the online database for one year after the date of fulfillment or release, the FDA.gov Archive was used to locate previous Postmarketing Study and Clinical Trial Requirements and Commitments Database Files. When archived databases with the final statuses were unavailable, we recorded the most recent status and date for each postmarketing requirement (e.g., "last available status: *Pending,* October 31, 2010"). We then performed additional Google searches using the terms "postmarketing" or "PMR" in combination with manufacturers names to determine whether manufacturers were publicly sharing their own information about postmarketing requirements (e.g., "Pfizer PMRs" or "Pfizer postmarketing requirements"). Lastly, we reviewed the supplemental letters on the Drugs@FDA database to determine whether they included information regarding the fulfillment of postmarketing requirements. The abstractions were performed by one reviewer (JDW). Consistency and accuracy were verified through a 10% random sample validation performed by a second reviewer (ACE).

Trial Registration and Results Reporting on ClinicalTrials.gov and Peer-Reviewed Publication

For all new prospective cohort studies, registries, and clinical trials and all requirements that call for the completion and submission of the results from 'ongoing' prospective cohort studies and trials (hereafter 'prospective cohort studies, registries, and clinical trials'), we determined study registration and results reporting on ClinicalTrials.gov.

One reviewer (JDW) entered the new drug or biologic names and study characteristics (e.g., indication, comparator, outcome, and population) based on the information available in the postmarket study descriptions into the advanced search feature of ClinicalTrials.gov. Nine criteria were used to match trial registrations with the postmarket study descriptions: (1) intervention, (2) indication, (3) similar ClinicalTrials.gov registration years and postmarketing requirement protocol submission years outlined in the FDA approval letters, (4) trial identification name/number provided in the postmarketing requirement descriptions, (5) industry sponsor funding source (yes, no), (6) comparator(s), (7) outcome(s), (8) study population, and (9) study duration. At a minimum, matches were required to fulfill criteria 1-3 or 4. A

third author (SSD) repeated all searches for trials that were determined to be unregistered. Potential matches not fulfilling criteria 1-4 were discussed with the senior investigator (JSR).

Once identified, for each registered prospective cohort study, registry, and clinical trial, one reviewer (JDW) abstracted study characteristics from the ClinicalTrials.gov registration, including: National Clinical Trial (NCT) number; ClinicalTrials.gov status (e.g., *Currently recruiting*, *Completed, Terminated, and Withdrawn*);[17] first submission, first results reporting, study start, and primary completion dates; estimated overall population; use of randomization; whether subject allocation was double or triple blind, single blind, or none/open-label; and whether there was a placebo, active, or no comparator. When postmarketing requirements did not specify a primary end point, we recorded the primary end point and corresponding duration provided in the ClinicalTrials.gov registration. Each primary end point was then classified as either a clinical outcome, clinical scale, surrogate outcome, or safety and tolerability outcome based on conventions used in prior research.[1 3]

For all postmarket prospective cohort studies, registries, and clinical trials with a *Completed* or *Terminated* status on ClinicalTrials.gov, for which results reporting would be expected, we recorded whether any study results were reported and/or corresponding articles were published. For all prospective cohort studies, registries, and clinical trials without publications listed on ClinicalTrials.gov and all unregistered prospective cohort studies, registries, and clinical trials classified as *Submitted, Fulfilled, Released,* or unclear (e.g., "last available status: *Pending,* October 31, 2010) according to FDA or drug sponsor data, one author (JDW) used a systematic two-step search strategy to locate publications, as has been done in prior research.[18] First, Google and the Scopus (Elsevier, Philadelphia, PA) and PubMed databases were searched using the NCT number. If a matching publication was not found, we searched for original research articles in the Scopus database using the terms "[intervention name]" and "clinical trial" in the "article title, abstract, keywords" field. For prospective cohort studies and registries, we searched for "[intervention]" and "registry" as well as "[intervention]" and "cohort". If necessary, we added "[indication]" to the search. We used five criteria to identify matching publications: study design, indication, intervention, primary outcome(s), and intention to treat enrollment, as has been done in prior

research.[18 19] If there were multiple publications, we used the date of the earliest publication that reported the primary results of the trial. A third author (SSD) repeated all searches for postmarketing requirements that were determined to be unpublished. Lastly, we extracted the date of first publication in a peer-reviewed journal and the 2015 journal impact factor according to InCites™ Journal Citation Reports. Consistency and accuracy were verified through a 10% random sample validation performed by a second reviewer (ACE). All uncertainties and disagreements were resolved by consensus with input from the senior investigator (JSR).

Patient involvement

No patients were involved in establishing the research question or outcome measures, designing or implementing the study, interpreting the results, or drafting the manuscript. There are no plans to disseminate the results to study participants or the relevant patient community.

Ethics and dissemination

As a cohort study using publicly available data, this study does not require research ethics approval.

Statistical Analysis

Using descriptive statistics, we characterized the new drugs and biologics and postmarket study characteristics. Fisher's exact and Kruskal-Wallis tests were used, as appropriate, to examine differences among postmarket study characteristics, including therapeutic area, orphan status, and postmarketing requirement category. To estimate time to "first results reported" (either on ClinicalTrials.gov or in a peer-reviewed publication), we generated Kaplan-Meier plots. Analyses were performed using R (version, 3.2.3; The R Project for Statistical Computing). All statistical tests were 2-tailed.

RESULTS

Characteristics of New Drugs and Biologics

Between 2009 and 2012, the FDA approved 110 new drugs and biologics for 120 indications, 13 (11.8%) of which did not have any postmarketing requirements at the time of first approval. The final study sample included 97 novel drugs and biologics for 106 indications (**Table 1**): 75 (77.3%) of which

were drugs and 22 (22.7%) were biologics. Drugs and biologics indicated for the treatment of cancer and hematology (26 [26.8%]) were the most common. Nearly one-third of the drugs (28 [28.9%]) received priority review and approximately one in ten (9 [9.3%]) received accelerated approval. There were 15 (15.5%) novel drugs and biologics that were designated as orphan products.

Postmarketing Requirements From 2009 Through 2012

There were 437 postmarketing requirements associated with these 97 new drugs and biologics. The median number of requirements per approval letter for each new drug or biologic was 4 (interquartile rage [IQR], 4-6), which was consistent between 2009 and 2012. Half of the postmarket studies required (220 [50.3%]) were for "new animal or 'other' studies" (**Table 2**) and nearly one-third were for prospective cohort studies, registries, and clinical trials (134 [30.7%]). More than three-quarters of postmarket studies were issued under FDAAA (344 [78.7%]) authority, more than one-sixth under PREA (77 [17.6%]) authority.

Individual postmarket study descriptions were often short and difficult to categorize **(see supplementary appendix box 2)**, with a median word count of 44 (IQR, 29-71). Among the 110 clinical trials, there was not enough information to establish use of randomization, comparator type, outcome, and allocation for 38 (34.5%), 44 (40.0%), 62 (56.4%) and 66 (60.0%), respectively (**see supplementary appendix table 1**).

Among the 437 postmarket studies overall, 166 (38.0%) were classified as *Fulfilled* according to FDA or drug sponsor data (**see supplementary appendix table 2**). One-third (44 [32.8%]) of the 134 postmarket prospective cohort studies, registries, and clinical trials were classified as either *Submitted* or *Fulfilled*. There were 50 postmarket studies, without an up-to-date status in any of the available Postmarketing Study and Clinical Trial Requirements and Commitments Database Files, that were classified as *Fulfilled* according to supplemental letters on Drugs@FDA. Drug sponsor data was available for 106 postmarketing requirements. Overall, there were 131 (30.0%) postmarket studies without enough information in any publicly available source to determine a recent, up-to-date status.

Prospective Cohort Studies, Registries, and Clinical Trials: Registration and Study Characteristics

Among the 134 postmarket prospective cohort studies, registries, and clinical trials, 102 (76.1%) were registered on ClinicalTrials.gov (**Table 3**); among the 110 studies explicitly described as clinical trials, 84 [76.4%]) were registered. Nearly all Accelerated Approval pathway (9 of 10 [90.0%]) and FDAAA (60 of 71 [84.5%]) studies were registered. Those for autoimmune, musculoskeletal, or dermatological indications were all registered (19 of 19 [100.0%]).

The majority of the 102 registered prospective cohort studies, registries, and clinical trials were randomized (67 [65.7%]) with open label allocation (56 [54.9%]); fewer than half were placebo controlled (41 [40.2%]) (**Table 4**). While safety and tolerability end points were used in nearly half of these studies (50 [49.0%]), only 15 (14.7%) focused on clinical outcomes. Median study duration and estimated sample size, according to the ClinicalTrial.gov registrations, were 12 months (IQR, 2.8-31.0) and 265.0 (83.5-690.5), respectively. Unlike FDAAA and PREA postmarketing requirements, all required postmarketing trials of agents approved through the Accelerated Approval pathway were randomized (56.7%, 72.7%, and 100.0%, respectively, $P = 0.01$). Over half of the studies used for cancer were for surrogate endpoints (11 of 19 [57.9%)], while the majority of those required under the FDAAA authority had safety and tolerability outcomes (40 of 60 [66.7%]).

Prospective Cohort Studies, Registries, and Clinical Trials: Results Reporting and Publication

Among the 50 prospective cohort studies, registries, and clinical trials classified as *Completed* or *Terminated* on ClinicalTrials.gov, 36 (72.0%) had reported results (**Table 3**); among the 46 clinical trials, 35 (76.1%) had reported results. Among the 65 registered or unregistered studies for which publication would be expected based on the most recent status provided by FDA, drug sponsors, or on ClinicalTrials.gov, 36 (55.4%) were published in the peer-reviewed literature and 47 (72.3%) had either reported results or were published. The median publication journal impact factor was 12.8 [IQR, 2.8-33.9]. Reporting and publication rates did not differ according to postmarketing requirement authority, therapeutic area, and orphan status.

The median time from FDA approval to reported results or publication of postmarket studies was 47 (IQR, 32-67) months. While one-third [15 (31.9%)] of postmarket studies reported public results ahead

of schedule (median 19 [IQR, 10-23] months before the FDA report submission deadline), two-thirds [32 (68.1%)] reported results behind schedule (median 14 [IQR, 7-14] months after the deadline). Half (51.7%) of all 134 required prospective cohort studies, registries, or clinical trials reported results on ClinicalTrials.gov or were published (Final follow-up November 15, 2017, **Figure 1**). Among the 47 postmarket studies registered on ClinicalTrials.gov that reported results or were published, the median time from estimated study completion according to ClinicalTrials.gov to results reporting or publication was 15 (IQR, 12-23) months.

Discussion

Among 97 new drugs and biologics approved by FDA between 2009 and 2012, we identified 437 associated postmarketing requirements issued by FDA at the time of approval, many of which were only briefly described and often did not contain enough public information to understand the purpose of the requirement or characterize the required study designs. Furthermore, we were unable to locate up-to-date information on the progress of approximately one-third. Focusing exclusively on prospective cohort studies, registries, and clinical trials, which are likely of greatest clinical importance to physicians and patients, we found evidence of successful dissemination of research findings: three-fourths were registered on ClinicalTrials.gov and nearly three-fourths had either reported results or were published. However, two-thirds of the postmarket studies reported results publicly after their original FDA report submission deadline, potentially limiting their application to clinical practice.

The brief descriptions of many postmarket clinical trials often did not contain enough information to establish use of randomization, comparator type, and allocation. Moreover, over half of all postmarketing requirements did not specify an endpoint, an essential feature to understand how the study might inform clinical practice. Detailed descriptions are also necessary to determine corresponding ClinicalTrials.gov registrations and journal publications. Our findings are consistent with a recent report published by the Office of Inspector General (OIG), which discussed difficulties classifying 37 postmarket studies and emphasized previous concerns related to the classification of postmarket study statuses.[10 20] Similar to the OIG, we found that approximately one-quarter of postmarketing requirements

were for new clinical trials. Additional categorization revealed that half of the postmarketing requirements were for new animal or 'other studies', including pharmacokinetic trials and in vitro or in vivo studies. Overall, our findings may suggest that manufacturers are given significant flexibility in designing studies, and that the majority of postmarket studies do not address clinical questions that are of greatest interest to physicians and patients.

Our study also found evidence of successful registration and dissemination of the results of postmarketing requirements for clinical studies. Approximately three-fourths were registered on ClinicalTrials.gov, similar to previously reported registration rates for clinical trials supporting New Drug Applications.[21 22] Our finding that nearly three-fourths of the postmarket studies had either reported results or were published is consistent with a recent study by FDA, which showed that nearly two-thirds of postmarket drug interventional clinical trials and other trials designated as "fulfilled" were published in either the scientific literature or on the ClinicalTrials.gov website.[11] However, only 55.5% of postmarket studies for which publication would be expected were published in peer-reviewed medical journals. This contrasts to prior research on trials supporting FDA approval of new drugs and biologics showing that nearly 90% were published in peer-reviewed journals.[19] Given the increasing importance of postmarket requirements adding to our understanding of safety and effectiveness of new drugs and biologics, even greater emphasis must be placed on registration, results reporting, and publication of all required postmarket studies.

Furthermore, the majority of postmarket studies reported public results after their original FDA report submission deadline. Although drug sponsors may be meeting FDA reporting deadlines, our work supports previous claims of the slow pace of postmarket studies.[10] More timely results reporting across all postmarketing requirement authorities is necessary to ensure that the findings from postmarket studies can inform clinical practice.

Implications and Recommendations

In the United States, expedited review pathways are being increasingly employed for approval of new drugs and biologics,[23] which can provide market authorization on the basis of less rigorous standards.

As FDA regulatory paradigms shift towards lifecycle evaluation, there will be an increasing reliance on data generated by postmarket studies. While more detailed postmarket study descriptions and increased FDA transparency are necessary, it is promising that the majority of postmarket prospective cohort studies, registries, and clinical trials are registered and have reported results or were published.

Our findings support a recent proposal for FDA reform, which outlined opportunities to enhance transparency at the FDA and suggested that FDA release the final reports that fulfill postmarketing requirements.[24] FDA already has higher standards for reviewing and publishing information on pediatric studies conducted under PREA and the Best Pharmaceutical for Children's Act, including publicly available medical, statistical, and clinical pharmacology reviews and information regarding the types of studies conducted (e.g. trial design, number of pediatric patients, etc.). In order to further strengthen postmarketing requirement transparency, all postmarket drug study descriptions should include a clear study design (e.g., animal trial, prospective cohort study, etc.), trial endpoint(s), potential comparator arm(s), study population(s), follow-up duration, and a target sample size. Recently, FDA announced a plan to add ClinicalTrials.gov NCT numbers to materials for future drug approvals.[25] FDA should consider expanding this initiative to add NCT numbers to postmarketing requirement descriptions and the Postmarketing Study and Clinical Trial Requirements and Commitments Database Files to make it easier for patients, physicians, and researchers to associate clinical trial listings to FDA documents for postmarket studies.

After reviewing publicly available FDA and drug sponsor data, we were only able to locate up-to-date statuses for two-thirds of the postmarket drug studies. FDA should consider making their Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), a non-publicly available database that includes information for all prescription drug postmarketing requirements, publicly available. In particular, DARRTs includes Annual Status Reports, which are the detailed reports that drug sponsors must submit annually to the FDA on the status of each open postmarketing requirement.[7] At a minimum, FDA should not remove "fulfilled" and "released" requirements from the Postmarketing Study and Clinical Trial Requirements and Commitments Database Files, rendering them no longer publicly

identifiable. Currently, these requirements are displayed on the website for "not more than 1 year from the data of fulfillment or releases."[6] FDA already provides more extensive information, including an extensive reporting schedule, for both active and inactive postapproval studies for medical devices.[26] Similar reporting standards could be adopted for drug and biologic postmarketing requirements. These, and other suggestions to promote transparency and improve the oversight of postmarketing requirements,[7 10 21] may be key to ensuring the successful translation of results from postmarket studies into clinical practice.

Limitations of this study

This study has limitations. First, our study relied on publicly available data sources. The brief postmarketing requirement descriptions provided in the FDA approval letters made categorizing postmarket drug studies and determining ClinicalTrials.gov registrations and peer-reviewed publications difficult. Furthermore, various versions of FDA's Postmarketing Study and Clinical Trial Requirements and Commitments Database Files were used to determine the final statuses of the postmarketing requirements. *Fulfilled* and *Released* requirements are only displayed on the online database for one year after the date of fulfillment or release and we were unable to locate archived databases for all years of follow-up. To account for this limitation, we searched for postmarketing requirement statuses provided in supplementary applications or online by drug sponsors. Furthermore, since DARRTS is not available to the public, the statuses of certain postmarketing requirements and our estimates regarding the timeliness of results dissemination may not be based on up-to-date data.[20] Second, while we focused on postmarketing requirements that were imposed between 2008 and 2012, potentially allowing for at least four years for completion and publication, our study did not account for the time that it might take to prepare and disseminate research findings.[27] In particular, once a postmarket study has been completed, authors need to prepare manuscripts, submit them to journals, revise, and potentially resubmit to multiple journals before acceptance. Although we looked for reported results and publications for all studies classified as *Completed* or *Terminated* on ClinicalTrials.gov, we acknowledge that additional studies may get published, but were not published at the time of our search. Third, we did not determine whether the

results from required 'ongoing' prospective cohort studies, registries, or clinical trials were reported or published. While some 'ongoing' studies may have reported or published results, ongoing studies are less likely to have results reported and publications.

Conclusions

Postmarketing requirements for new drugs and biologics were often briefly described, difficult to categorize, and frequently did not contain enough information to characterize the required study designs. Nearly three-fourths of postmarket prospective cohort studies, registries, and clinical trials, which are often the greatest interest to clinicians and patients, were registered on ClinicalTrials.gov or had either reported results or were published. However, two-thirds of the postmarket studies reported public results after their original FDA report submission deadline. These findings highlight the need for more detailed postmarket study descriptions, increased FDA transparency, and clearer and more consistent registration and results reporting standards.

ACKNOWLEDGEMENTS

Contributors: JDW, ACE, and JSR conceived and designed this study. JDW, ACE, and SSD acquired the data. JDW conducted the statistical analysis and drafted the manuscript. All authors participated in the interpretation of the data and critically revised the manuscript for important intellectual content. JDW and JSR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JSR provided supervision. JDW and JSR are guarantors.

Funding: This project was conducted as part of the Collaboration for Research Integrity and Transparency (CRIT) at Yale, funded by the Laura and John Arnold Foundation, which supports JDW, ACE, MEM, and JSR. The Laura and John Arnold Foundation played no role in the design of the study, analysis or interpretation of findings, or drafting the manuscript and did not review or approve the manuscript prior to submission. SSD is supported by the Robert Wood Johnson Foundation Clinical Scholars Program and the Department of Veterans Affairs. JEM receives funding from the Laura and John Arnold Foundation. The authors assume full responsibility for the accuracy and completeness of the ideas presented.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: In the past 36 months, JDW received research support through the Meta Research Innovation Center at Stanford (METRICS) from the Laura and John Arnold Foundation. JSR received research support through Yale from Johnson and Johnson to develop methods of clinical trial data sharing, from Medtronic, Inc. and the Food and Drug Administration (FDA) to develop methods for postmarket surveillance of medical devices (U01FD004585), from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, from the FDA to establish a Center for Excellence in Regulatory Science and Innovation (CERSI) at Yale University and the Mayo Clinic (U01FD005938), from the Blue Cross Blue Shield Association to better understand medical technology evaluation, and from the Agency for Healthcare Research and Quality (R01HS022882). SSD receives support as a Scholar in the Yale University / Mayo Clinic FDA CERSI. LS and SW were cofounders of Informulary, Inc., a company that proved data and

the benefits, harms, and uncertainties of prescription drugs. The company has ceased operations. LS and SW report personal fees from Ross Feller Case, LLP, outside the submitted work. JEM receives funding from the Laura and John Arnold Foundation.

Ethical approval: As a cohort study using publicly available data, this study does not require research ethics approval.

Data sharing: Requests for collected data can be made to the corresponding author at Joshua.wallach@yale.edu

Transparency: JDW and JSR, on behalf of the authors, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant registered) have been explained.

REFERENCES

1. Downing NS, Aminawung JA, Shah ND, et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA* 2014;311(4):368-77. doi: 10.1001/jama.2013.282034

2. Psaty BM, Meslin EM, Breckenridge A. A lifecycle approach to the evaluation of FDA approval methods and regulatory actions: opportunities provided by a new IOM report. *JAMA* 2012;307(23):2491-2. doi: 10.1001/jama.2012.5545

3. Pease AM, Krumholz HM, Downing NS, et al. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ* 2017;357:j1680. [published Online First: 2017/05/03]

4. Institute of Medicine. The future of drug safety: promoting and protecting the health of the public. http://www.nap.edu/catalog.php?record_id=11750. Accessed 1 June 2017.

5. US Food And Drugs Administration (FDA). Postmarket drug and biologic safety evaluations. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm.

6. U.S. Food and Drug Administration. Postmarketing Requirements and Commitments (FAQ). https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm. Accessed 5 Dec 2017.

7. Department of Health and Human Services Office of Inspector General. FDA is Issuing More Postmarketing Requirements, but Challenges with Oversight Persist. https://oig.hhs.gov/oei/reports/oei-01-14-00390.pdf, July 2016. Accessed 10 Nov 2017.

8. Fain K, Daubresse M, Alexander GC. The Food and Drug Administration Amendments Act and postmarketing commitments. *JAMA* 2013;310(2):202-4. doi: 10.1001/jama.2013.7900

9. Naci H, Wouters OJ, Gupta R, et al. Timing and Characteristics of Cumulative Evidence Available on Novel Therapeutic Agents Receiving Food and Drug Administration Accelerated Approval. *Milbank Q* 2017;95(2):261-90. doi: 10.1111/1468-0009.12261

10. Woloshin S, Schwartz LM, White B, et al. The Fate of FDA Postapproval Studies. *N Engl J Med* 2017;377(12):1114-17. doi: 10.1056/NEJMp1705800

11. Cruz ML, Xu J, Kashoki M, et al. Publication and Reporting of the Results of Postmarket Studies for Drugs Required by the US Food and Drug Administration, 2009 to 2013. *JAMA Intern Med* 2017;177(8):1207-10. doi: 10.1001/jamainternmed.2017.1313

12. U.S. Food and Drug Administration (FDA). Drugs@FDA: FDA Approved Drug Products. FDA website. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed April 1, 2017.

13. U.S. Food and Drug Administration. Priority review. https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm. Updated September 15, 2014. Accessed 1 April 2017. .

14. World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology. ATC/DDD index 2017. https://www.whocc.no/atc_ddd_index/ .

15. Food and Drug Administration Amendments Act of 2007. US Public Law 110-85. (2007, Sept 27); 21 USC 301.

16. U.S. Food and Drug Administration (FDA). Postmarket Requirements and Commitments. FDA website. http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm. Accessed April 1, 2017.

17. ClinicalTrials.gov. Glossary of Common Site Terms. https://clinicaltrials.gov/ct2/about-studies/glossary. Accessed 1 April 2017.

18. Chen R, Desai NR, Ross JS, et al. Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers. *BMJ* 2016;352:i637. [published Online First: 2016/02/17]

19. Smithy JW, Downing NS, Ross JS. Publication of pivotal efficacy trials for novel therapeutic agents approved between 2005 and 2011: a cross-sectional study. *JAMA Intern Med* 2014;174(9):1518-20. doi: 10.1001/jamainternmed.2014.3438

20. Kashoki M, Lee C, Stein P. FDA Oversight of Postmarketing Studies. *N Engl J Med* 2017;377(12):1201-02. doi: 10.1056/NEJMc1709185

21. Miller JE, Wilenzick M, Ritcey N, et al. Measuring clinical trial transparency: an empirical analysis of newly approved drugs and large pharmaceutical companies. *BMJ Open* 2017;7(12):e017917. doi: 10.1136/bmjopen-2017-017917 [published Online First: 2017/12/05]

22. Miller JE, Korn D, Ross JS. Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. *BMJ Open* 2015;5(11):e009758. doi: 10.1136/bmjopen-2015-009758 [published Online First: 2015/11/12]

23. Kesselheim AS, Wang B, Franklin JM, et al. Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ* 2015;351:h4633. [published Online First: 2015/09/23]

24. Sharfstein JM, Stebbins M. Enhancing Transparency at the US Food and Drug Administration: Moving Beyond the 21st Century Cures Act. *JAMA* 2017;317(16):1621-22. doi: 10.1001/jama.2017.2481

25. U.S. Food and Drug Administration Statement. FDA Commissioner Scott Gottlieb, M.D., on new steps FDA is taking to enhance transparency of clinical trial information to support innovation and scientific inquiry related to new drugs. 16 Jan 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592566.htm. Accessed 28 Jan 2017.

26. U.S. Food and Drug Administration (FDA). Post-Approval Studies (PAS). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?s=c. Accessed 1 Jan 2018.

27. Wallach J, Egilman A, Gopal A, et al. Biomedical journal speed and efficiency: a cross-sectional pilot survey of author experiences. *Research Integrity and Peer Review* 2018;3(1) doi: doi.org/10.1186/s41073-017-0045-8

28. U.S. Food and Drug Administration (FDA). Expedited programs for serious conditions - drugs and biologics. https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf. Accessed 10 Sept 2017.

29. ClinicalTrials.gov. FDAAA 801 requirements. http://clinicaltrials.gov/ct2/manage-recs/fdaaa -/WhichTrialsMustBeRegistered.

FIGURE LEGEND

Figure 1. Proportion of Required Prospective Cohort Studies, Registries, and Clinical Trials of New Drugs and Biologics Approved by the Food and Drug Administration Between 2009 and 2012, According to Postmarketing Requirement Authority. PREA = Pediatric Research Equity Act and FDAAA = Food and Drug Administration Amendments Act of 2007.

Box 1. FDA Postmarketing Requirement Authorities			
Authority	**Year implemented**	**Purpose**	**Requirement**
Accelerated Approval pathway	1992	To expedite the approval of novel drugs that treat serious diseases and that fill unmet medical needs on the basis of surrogate or intermediate endpoints "reasonably likely" to predict clinical benefit.[28]	FDA has the authority to require postmarket studies or clinical trials to confirm efficacy.[28]
Animal Efficacy Rule	2002	To allow for the approval of novel drugs when human efficacy studies and field trials are not ethical and feasible.	When feasible and ethical, FDA can require postmarket studies in humans.
Pediatric Research Equity Act (PREA)	2003	To provide pediatric use information in drug product labeling for drugs and biological products developed for indications that occur in both adult and pediatric populations. FDA can approve novel drugs for use in adults without corresponding studies for the same indication in the relevant pediatric population.	FDA can include deferred pediatric studies or clinical trials as postmarketing requirements.
Food and Drug Administration Amendments Act (FDAAA) Section 505(o)(3)	2007[a]	To provide additional information for novel therapeutics approved under section 505 of FDAAA or section 351 of the Public Health Services Act.[6]	FDA can require postmarket studies that assess know serious risks, signs of serious risks, or unexpected serious risked related to the use of a novel drug.
[a] This authority became effective on March 25, 2008.			

Box 2. Postmarking requirement categorization
New prospective cohort studies, registries, and clinical trials [a]
Postmarketing requirements that outline *new* randomized controlled trials or other clinical trials evaluating safety and efficacy; prospective cohort studies and registries.
Complete or submit results from ongoing prospective cohort studies, registries, and clinical trials
Instead of requesting a *new* prospective study or trial, these postmarketing requirements call for the completion and submission of the results from 'ongoing' prospective cohort studies or trials.
New retrospective observational studies
Postmarketing requirements that outline *new* case-control, cross-sectional, and retrospective cohort studies; analyses of spontaneous adverse event reporting data.
New animal or "other" studies required
Postmarketing requirements that outline *new* animal trials; pharmacokinetic and/or pharmacodynamics trials; in vitro or in vivo studies; drug transport, drug-drug or drug-therapeutic, prenatal and postnatal development, assessments of anti-drug antibody response, mass balance, dosing, lactation, and QT/QTc studies.
Analyze/follow-up from observational studies, registries, or clinical trials (and other flexible requirements) [b]
Postmarketing requirements that outline longer follow-up or new analyses of data from existing trials or studies; submission of a final report for ongoing case-control, cross-sectional, or retrospective cohort studies; studies or trials that can be done as expansions of the previous observational studies; and postmarketing requirements that require the enrollment of additional patients in an existing registry.
Analyze/follow-up from an existing animal or "other" studies (and other flexible requirements) [b]
Instead of requesting a *new* animal or "other" study, these PMRs call for the submission of a final report for an ongoing "other" or animal study (category D); planned "other" studies that have already been outlined or proposed.
[a] This generally includes "controlled clinical investigation(s), other than phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of this Act."[15] Under FDAAA 801, only "applicable clinical trials" are required to submit information to ClinicalTrials.gov. These trials should have "either initiated as of September 27. 2007, or initiated before that date but are still ongoing as of December 2007," and meet one of the following conditions: A) The trial has one or more sites in the USA; B) The trial is conducted under an FDA investigation new drug application (IND); or C) The trial involves a drug or biological that is manufactured in the USA or its territories and is exported for research.[29] Since there may be inconsistent registration and results reporting of pharmacokinetic and phase 1 trial data on ClinicalTrials.gov, we did not classify trials that only evaluated pharmacokinetics under categories A or B. [b.] Some postmarketing requirements include flexible requirements that can be satisfied in multiple ways. A flexible postmarketing requirement could outline that drug manufacturers have the option of collecting safety data from an open-label extension of a clinical trial that the manufacturer has already committed to perform, from separate longer-term open-label safety trials, or from long-term controlled safety and efficacy trials.

Table 1. Characteristics of 97 New Drugs and Biologics Approved by the US Food and Drug Administration from 2009 Through 2012 with At Least One Postmarketing Requirement	
Characteristic	**No. (%)**
Approval year	
2009	23 (23.7)
2010	18 (18.6)
2011	25 (25.8)
2012	31 (32.0)
Class	
Drug	75 (77.3)
Biologic	22 (22.7)
Therapeutic area	
Cancer and hematology	26 (26.8))
Infectious disease	9 (9.3)
Cardiovascular, diabetes, and hyperlipidemia	10 (10.3)
Autoimmune, musculoskeletal, and dermatology	16 (16.5)
Neurology and psychiatry	13 (13.4))
Other	25 (25.8)
Priority review	
Yes	28 (28.9)
No	69 (71.1)
Accelerated Approval	
Yes	9 (9.3)
No	88 (90.7)
Orphan Drug	
Yes	15 (15.5)
No	82 (84.5)

Table 2. Categories and Authorities of Postmarketing Requirements for New Drugs and Biologics Approved by the US Food and Drug Administration Between 2009 and 2012.

	No. (%)				
	Authority				
Postmarketing Requirement Description	FDAAA	PREA	Accelerated approval	Animal efficacy rule	Total
New prospective cohort studies, registries, and clinical trials	59 (49.6)	53 (44.5)	7 (5.9)	0 (0.0)	119 (27.2)
Complete or submit results from prospective cohort studies, registries, and trials	12 (80.0)	0 (0.0)	3 (20.0)	0 (0.0)	15 (3.4)
New retrospective observational studies	19 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (4.4)
New animal or "other" studies	197 (89.5)	20 (9.1)	2 (0.9)	1 (0.5)	220 (50.3)
New or analyze/follow-up from observational studies or trials	41 (87.2)	3 (6.4)	3 (6.4)	0 (0.0)	47 (10.8)
New or analyze/follow-up from an existing animal or "other" studies	16 (94.1)	1 ((5.9)	0 (0.0)	0 (0.0)	17 (3.9)
Total	344 (78.7)	77 (17.6)	15 (3.4)	1 (0.2)	437

Table 3. Registration, Results Reporting, and Publication of Postmarketing Requirements of New Drugs and Biologics Approved by the Food and Drug Administration Between 2009 and 2012

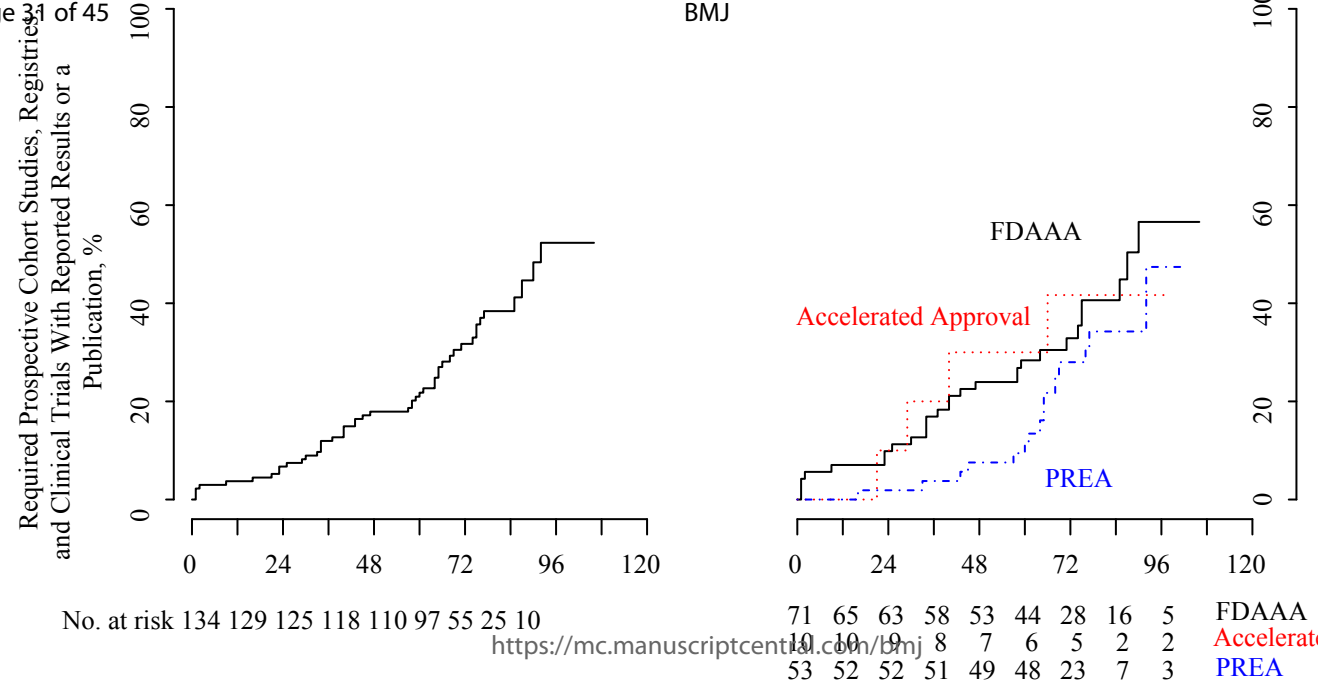
	No. (%)						
	Registration		**Results reporting**		**Publication[a] or results reporting**		
Category	**Eligible for registration ClinicalTrials.gov**	**Registered**	**Eligible for results reporting [b]**	**Results reported**	**Eligible for publication [c]**	**Published**	**Results reported or published**
Prospective cohort studies, registries, and clinical trials	134	102 (76.1)	50	36 (72.0)	65	36 (55.4)	47 (72.3)
Authority							
FDAA	71	60 (84.5)	31	23 (74.2)	37	22 (59.5)	28 (75.7)
PREA	53	33 (62.3)	16	11 (68.8)	22	11 (50.0)	15 (68.2)
AA	10	9 (90.0)	3	2 (66.7)	6	4 (66.7)	4 (66.7)
P value		.01		.88		.70	.70
Therapeutic area							
Cancer and hematology	26	19 (73.1)	8	6 (75.0)	15	6 (40.0)	11 (73.3)
Infectious disease	19	16 (84.2)	9	6 (66.7)	12	7 (58.3)	9 (75.0)
Cardiovascular, diabetes, and hyperlipidemia	14	11 (78.6)	5	5 (100.0)	6	3 (50.0)	5 (83.3)
Autoimmune, musculoskeletal, and dermatology	19	19 (100.0)	11	9 (81.8)	11	6 (54.5)	9 (81.8)
Neurology and psychiatry	26	17 (65.4)	8	4 (50.0)	11	5 (45.5)	6 (54.5)
Other	30	20 (60.7)	9	6 (66.7)	10	5 (50.0)	7 (70.0)
P value		.04		.50		.76	.81
Orphan designation							
Yes	14	12 (85.7)	8	7 (87.5)	8	7 (87.5)	7 (87.5)
No	120	90 (75.0)	42	29 (69.0)	57	30 (52.6)	40 (70.2)
P value		.52		.41		.12	.43

[a] "Publication" indicates publication in the peer-reviewed literature.
[b] Prospective cohort studies, registries, and clinical trials classified as *Completed* or *Terminated* by ClinicalTrials.gov.
[c] When information was available from a ClinicalTrials.gov registration, the denominator included *Completed* and *Terminated* prospective cohort studies, registries, or clinical trials. For registered and unregistered prospective cohort studies, registries, or clinical trials, we used information provided by FDA or drug sponsors on the status of the postmarketing requirements. We searched for publications for prospective cohort studies, registries, and clinical trials classified by the FDA as *Submitted, Fulfilled,* or *Released.* We also searched for publications for postmarketing requirements where the last status provided by the FDA was unclear (e.g., last available record: 2013, ongoing).

Table 4. Study Characteristics of Registered Prospective cohort studies, Registries, and Clinical Trials Based on ClinicalTrials.gov Data

	No. (%)											Median (IQR)[a]	
		Allocation			Comparator			End Point				Estimated Sample Size	Duration (months)
Registered Postmarketing Requirements	**Randomized**	**Double Blind**	**Single Blind**	**Open label**	**Placebo**	**Active**	**None**	**Surrogate Outcome**	**Clinical Outcome**	**Clinical Scale**	**Safety and tolerability**		
All (n=102)	67 (65.7)	42 (41.2)	4 (3.9)	56 (54.9)	41 (40.2)	22 (21.6)	39 (38.2)	29 (28.4)	15 (14.7)	8 (7.8)	50 (49.0)	265.0 (83.5-690.5)	12.0 (2.8-31.0)
Authority													
FDAAA (n=60)	34 (56.7)	22 (36.7)	0 (0.0)	38 (63.3)	20 (33.3)	12 (20.0)	28 (46.7)	12 (20.0)	7 (11.6)	1 (1.7)	40 (66.7))	430.5 (162.0-1176.0)	14.2 (6.0-48.0)
PREA (n=33)	24 (72.7)	18 (54.6)	4 (12.1)	11 (33.3)	16 (48.5)	6 (18.2)	11 (33.3)	9 (27.3)	7 (21.2)	7 (21.2)	10 (30.3)	150.0 (50.0-260.0)	2.8 (1.4-6.0)
AA (n=9)	9 (100.0)	2 (22.2)	0 (0.0)	7 (77.8)	5 (5.6)	4 (44.4)	0 (0.0)	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	347.0 (300.0-452.0)	31.0 (25.8-60.0)
P value	.02	.004			.04			< .001				.001	<0.001
Therapeutic Area													
Cancer and hematology (n=19)	15 (79.0)	5 (26.3))	0 (0.0)	14 (73.7)	5 (26.3)	5 (26.3)	9 (47.4)	11 (57.9)	5 (26.3)	0 (0.0)	3 (15.8)	437.0 (186.0-811.5)	29.3 (12.0-48.0)
Infectious disease (n=16)	9 (56.3)	4 (25.0)	3 (18.8)	9 (56.3)	2 (12.5)	6 (37.5)	8 (50.0)	4 (25.0)	3 (18.8)	0 (0.0)	9 (56.3)	152.5 (41.0-306.0)	5.5 (1.2-11.3)
Cardiovascular, diabetes, and hyperlipidemia (n=11)	9 (81.8)	8 (72.7)	0 (0.0)	3 (27.3)	2 (18.2)	8 (72.7)	1 (9.1)	5 (45.5)	0 (0.0)	0 (0.0)	6 (54.5))	3190.0 (365-8045.0)	34.8 (4.8-80.2)
Autoimmune, musculoskeletal, dermatology (n=19)	12 (63.2)	8 (42.1)	0 (0.0)	11 (57.9)	3 (15.8)	8 (42.1)	8 (42.1)	3 (15.8)	2 (10.5)	2 (10.5)	12 (63.2)	265.0 (95.5-1180.0)	12.0 (7.8-36.7)
Neurology and psychiatry (n=17)	10 (58.8)	10 (58.8)	0 (0.0)	7 (41.2)	10 (58.8)	4 (23.5)	3 (17.7))	0 (0.0)	3 (17.7)	5 (29.4)	9 (52.9)	306.0 (118.0-400.0)	2.8 (1.6-22.0)
Other (n=20)	12 (60.0)	7 (35.0)	1 (5.0)	12 (60.0)	8 (40.0)	2 (10.0)	10 (50.0)	6 (30.0)	2 (10.0)	1 (5.0)	11 (55.0)	173.5 (74.3-300.0)	10.5 (3.1-27.0)
P value	.55	< .001			<0.001			< .001				.01	.006
Orphan Designation													
Yes (n=12)	8 (66.7)	3 (25.0)	0 (0.0)	9 (75.0)	2 (16.7)	4 (33.3)	6 (50.0)	5 (41.7)	3 (25.0)	0 (0.0)	4 (33.3)	312 (206.5-429.0)	12.9 (10.5-28.1)
No (n=90)	59 (65.6)	39 (43.4))	4 (4.4)	47 (52.2)	39 (43.3)	18 (20.0)	33 (36.7)	24 (26.7)	12 (13.3)	8 (8.9)	46 (51.1)	255.0 (83.5-748.0)	11.5 (2.8-31.0)
P value	1.0	.38			0.20			.34				.86	.48

[a] Based on Kruskal-Wallis test



Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved Between 2009 and 2012: a Cross-Sectional evaluation

Study protocol (November 5th 2017)

Joshua D Wallach; Alexander C Egilman; Sanket S Dhruva, Margaret E McCarthy; Jennifer E Miller; Steven Woloshin; Lisa M Schwartz; Joseph S Ross

AIMS

This analysis characterizes all postmarketing requirements (PMRs) outlined in the original FDA approval letters for all novel therapeutic agents – pharmacologics and biologics – approved between 2009 and 2012 with at least one PMR. In particular, we sought to evaluate the different types of required studies under the four separate FDA authorities; the status of these PMRs; and the rates of (1) registration and reporting of PMR results on ClinicalTrials.gov and (2) publication of PMR clinical trials in peer-review journals.

METHODS

Data Sources

Drugs@FDA is a publicly accessible database that is available through the FDA's website. It lists regulatory actions, such as approvals, for all recently approved prescription agents. The records for each approved agent are hyperlinked to FDA medical reviews, which are documents that outline the clinical evidence used to establish the efficacy and safety of the novel agent prior to approval. The Postmarket Requirements and Commitments database is also publicly accessible through the FDA's website and can be used to determine descriptions, schedules for completing, and characterizations of the current status of PMRs. It is updated once per quarter, at the end of January, April, July, and October, based on a review of Annual Status Reports (ASRs) submitted to FDA annually by drug sponsors. The most recent version of the Postmarket Requirements and Commitments database (July 31, 2017) was downloaded on August 10, 2017.

PROTOCOL MODIFICATION: The most recent version of the database (October 31, 2017) was downloaded on November 10, 2017.

Sample Construction

We identified all novel therapeutics (i.e., new molecular entities or novel biologic drugs) first approved between January 1, 2009, and December 31, 2012, excluding generic drugs, reformulations, and combination therapies of non-novel therapeutic agents, using a previously described approach. [13 13] We selected 2012 as a cut-off date to allow for at least four years for completion of PMRs.

Therapeutic Agent and Indication Characteristics

The Drugs@FDA database was used to categorize each novel therapeutic agent by year of approval and as a pharmacologic entity (small molecule) or biologic. Agents were also classified by orphan status, using previously described approach.[3] FDA approval letters were then used to determine the indications for which all novel therapeutic agents were initially approved for use, whether agents were approved through the Accelerated Approval (AA) pathway, and whether applications were designated by the FDA for priority or standard review. The Fast Track designation, which provides enhanced communication with FDA during the development process, and the Breakthrough Therapy designation, which was not implemented until 2014, were not assessed in this study.[3] The World Health Organization's Anatomic Therapeutic Classification system was used to categorize each indication into one of four therapeutic areas (cancer, cardiovascular disease and diabetes mellitus, infectious disease, and other).[14]

PROTOCOL MODIFICATION: Indications were then grouped into one of six therapeutic areas (cancer; infectious disease; cardiovascular disease and diabetes mellitus; autoimmune, musculoskeletal, and dermatology; neurology and psychiatry; and other).[14]

Identifying Postmarketing Requirements and Postmarketing Requirements Features

For each novel therapeutic agent, 1 reviewer (JDW) abstracted all AA, Pediatric Research Equity Act (PREA), Animal Efficacy Rule (AER), and Postmarketing requirements under 505(o)(3) (hereafter "FDAAA PMRs") PMRs from the approval letters hyperlinked in the Drugs@FDA database. The approval letters for novel therapeutics with PMRs include distinct sections that outline the required studies under each of the four possible authorities (e.g., "Required Pediatric Assessments"). For each

PMR, we abstracted the text outlining the requirement and the dates of final protocol submission, trial completion, and final report submission, when they were provided. We then classified each PMR as one of the six study categories outlined in **Box 1**. For all categories, we used strict classification criteria when only limited information was available. For example, a one sentence PMR outlining that a trial should evaluate pharmacokinetic outcomes would receive a category D (*New animal or "other" study require)* classification, since the outcome is unclear and there may be inconsistent registration and results reporting of pharmacokinetic and phase 1 trial data on ClinicalTrials.gov. However, a PMR description of a trial evaluating "PK, safety, and efficacy" would receive a category A (*New prospective cohort studies or trials)* classification However, if more information became available from a ClinicalTrials.gov registration or a corresponding publication, we used that information to improve the fidelity of our categorization. Consistency and accuracy were verified through a 10% random sample validation performed by a second reviewer (ACE).

PROTOCOL MODIFICAION: Using only the information from FDA approval letters hyperlinked in the Drugs@FDA database, we calculated the length of each postmarket study description (word count) and abstracted whether there was information provided about the use of randomization; whether patient allocation was double blind, single blind, open-label, or unclear; whether there was a comparator; whether the comparator was placebo, active control, both, or unclear; and study duration.

Box 1. Postmarking requirement categorization
New prospective cohort studies, registries, and clinical trials [a]
Postmarketing requirements that outline *new* randomized controlled trials or other clinical trials evaluating safety and efficacy; prospective cohort studies and registries.
Complete or submit results from ongoing prospective cohort studies, registries, and clinical trials
Instead of requesting a *new* prospective study or trial, these postmarketing requirements call for the completion and submission of the results from 'ongoing' prospective cohort studies or trials.
New retrospective observational studies
Postmarketing requirements that outline *new* case-control, cross-sectional, and retrospective cohort studies; analyses of spontaneous adverse event reporting data.
New animal or "other" studies required
Postmarketing requirements that outline *new* animal trials; pharmacokinetic and/or pharmacodynamics trials; in vitro or in vivo studies; drug transport, drug-drug or drug-therapeutic,

prenatal and postnatal development, assessments of anti-drug antibody response, mass balance, dosing, lactation, and QT/QTc studies.
Analyze/follow-up from observational studies, registries, or clinical trials (and other flexible requirements)[b]
Postmarketing requirements that outline longer follow-up or new analyses of data from existing trials or studies; submission of a final report for ongoing case-control, cross-sectional, or retrospective cohort studies; studies or trials that can be done as expansions of the previous observational studies; and postmarketing requirements that require the enrollment of additional patients in an existing registry.
Analyze/follow-up from an existing animal or "other" studies (and other flexible requirements)[b]
Instead of requesting a *new* animal or "other" study, these PMRs call for the submission of a final report for an ongoing "other" or animal study (category D); planned "other" studies that have already been outlined or proposed.
[a] This generally includes "controlled clinical investigation(s), other than phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of this Act."[15] Under FDAAA 801, only "applicable clinical trials" are required to submit information to ClinicalTrials.gov. These trials should have "either initiated as of September 27. 2007, or initiated before that date but are still ongoing as of December 2007," and meet one of the following conditions: A) The trial has one or more sites in the USA; B) The trial is conducted under an FDA investigation new drug application (IND); or C) The trial involves a drug or biological that is manufactured in the USA or its territories and is exported for research.[29] Since there may be inconsistent registration and results reporting of pharmacokinetic and phase 1 trial data on ClinicalTrials.gov, we did not classify trials that only evaluated pharmacokinetics under categories A or B. [b.] Some postmarketing requirements include flexible requirements that can be satisfied in multiple ways. A flexible postmarketing requirement could outline that drug manufacturers have the option of collecting safety data from an open-label extension of a clinical trial that the manufacturer has already committed to perform, from separate longer-term open-label safety trials, or from long-term controlled safety and efficacy trials.

Status of Postmarketing Studies

The Postmarket Requirements and Commitments database was used to determine the status for each PMR. FDA assigns each PMR to one of the following seven status categories: *Pending* (the study or clinical trial has not been initiated (i.e., no subjects have been enrolled or animals dosed), but it does not meet the criterion for delayed); *Ongoing* (the study or clinical trial is proceeding according to, or ahead of, the original schedule. FDA considers a PMR to be ongoing until a final report is submitted and as long as the PMR status is not delayed or terminated); *Delayed* (the progression of the study or clinical trial is behind the original schedule); *Terminated* (the sponsor ended the study or clinical trial before completion and has not submitted a final report to FDA); *Submitted* (the sponsor has concluded or terminated the study or clinical trial and has submitted a final report to FDA, but FDA has not yet notified the sponsor

that the PMR is fulfilled, not fulfilled, or released); *Fulfilled* (the sponsor has submitted the final report, and FDA has reviewed the report and notified the sponsor in writing that the terms of the PMR have been met); or *Released* (FDA informed the sponsor in writing that it is released from its obligation to conduct the study or clinical trial). Considering that *Fulfilled* and *Released* requirements are only displayed on the online database for a year after the date of fulfillment or released, the FDA.gov Archive was used to locate previous Postmarket Requirements and Commitments database files. When archived databases with the final statuses were unavailable, we recorded the most recent status and date for each PMR (e.g., "last available status: *Pending,* October 31, 2010). We then performed additional Google searches using the terms "postmarketing" or "PMR" in combination with drug sponsors names to determine whether drug manufacturers were publicly sharing their own information about the status of their PMRs (i.e., "Pfizer PMRs" or "Pfizer postmarketing requirements"). The abstractions were performed by one reviewer (JDW). Consistency and accuracy were verified through a 10% random sample validation performed by a second reviewer (ACE).

PROTOCOL MODIFICATION: Lastly, we reviewed the supplemental letters on the Drugs@FDA database to determine whether they included information regarding the fulfillment of postmarketing requirements. The abstractions were performed by one reviewer (JDW). Consistency and accuracy were verified through a 10% random sample validation performed by a second reviewer (ACE).

Rates of Registration and Reporting of Clinical Trials on ClinicalTrials.gov and Peer-Reviewed Publication

For all PMRs outlining a new or the submission/completion of prospective cohort studies or clinical trials (categories A and B), we determined registration on ClinicalTrials.gov. One reviewer (JDW) entered drug names and multiple combinations of study characteristics based on the information available in the PMR descriptions (e.g., indication, comparator, outcome, population) into the advanced search feature of ClinicalTrials.gov. Nine criteria were used to match trial registrations with the PMR study descriptions: (1) intervention, (2) indication, (3) funding (industry), (4) similar registration and

PMR protocol submission dates, (5) trial identification number, (6) comparator(s), (7) outcome(s), (8) study population, and (9) length. At a minimum, matches were required to fulfill criteria 1-4. Consistency and accuracy were again verified through a 10% random sample validation performed by a second reviewer (ACE). A third author (SD) repeated all searches for trials that were determined to be unregistered. All potential matches fulfilling different combinations of criteria 1-8 were discussed with the senior investigator (JSR) before final classifications were made.

PROTOCOL MODIFICATION: Nine criteria were used to match trial registrations with the postmarket study descriptions: (1) intervention, (2) indication, (3) similar ClinicalTrials.gov registration years and postmarketing requirement protocol submission years outlined in the FDA approval letters, (4) trial identification name/number provided in the postmarketing requirement descriptions, (5) industry sponsor funding source (yes, no), (6) comparator(s), (7) outcome(s), (8) study population, and (9) study duration. At a minimum, matches were required to fulfill criteria 1-3 or 4. A third author (SSD) repeated all searches for trials that were determined to be unregistered. Potential matches not fulfilling criteria 1-4 were discussed with the senior investigator (JSR).

Once identified, for each registered trial, we collected the National Clinical Trial number (NCT number), the ClinicalTrials.gov status (e.g., *currently recruiting*, *completed, withdrawn*), and the dates for first submitted, results first posted, start, and primary completion. For PMRs that did not specify a primary outcome, we recorded the primary outcome(s) and corresponding duration provided in the ClinicalTrials.gov registration. For PMRs outlining the completion or submission of results from prospective cohort studies or trials for a specific outcome, we recorded the duration based on the PMR text. From the ClinicalTrials.gov registrations, we also abstracted the estimated or total study sample, allocation (randomized or non-randomized), whether there was masking (e.g., double or triple, single, or none/open-label), the comparator, and the comparator classification (None, Placebo, Active, Active and placebo, none, Multi-dose no comparator, Multi-dose and active, or Multi-dose and placebo).

To determine publications rates for all prospective cohort studies or clinical trials classified as *completed* or *terminated* on ClinicalTrials.gov, we recorded whether any corresponding publications and study results were available on ClinicalTrials.gov. One author (JDW) then used a systematic two-step search strategy to locate publications not listed on ClinicalTrials.gov. Firstly, Google and the Scopus (Elsevier, Philadelphia, PA) and PubMed databases were searched using the NCT number. If a matching publication was still not found, we searched for original research articles in the Scopus database using the terms "[intervention name]" and "clinical trial" in the "article title, abstract, keywords" field. If necessary, we added "[indication]" to the search. Scopus was selected because it is one of the most comprehensive databases available, as has been done in prior research (cite publication and reporting of clinical trial results Chen). We used five criteria to identify matching publications: study design, indication, intervention, primary outcomes, and intention to treat enrollment, as has been done in prior research. If there were multiple publications, we used additional criteria including primary investigators and study locations to identify a matching publication. If there were multiple publications, we used the date of the earliest publication that reported the primary results of the trial. For all trials without ClinicalTrials.gov registrations, we performed Scopus searches to locate potential publications. Consistency and accuracy were again verified through a 10% random sample validation performed by a second reviewer (ACE). A third author (SD) repeated all searches for PMRs that were determined to be unpublished. All uncertainties and disagreements will be resolved by consensus with input from the senior investigator (JSR).

Ethics and dissemination

As a cohort study on PMRs, this study does not require research ethics approval. The results will be presented at relevant national and international conferences as well as published in a peer-reviewed scientific journal.

Statistical Analysis

Using descriptive statistics, we characterized the novel therapeutic agents included in our sample and the indications for which they were initially approved. Next, we used descriptive statistics to

characterize the PMRs across the overall sample. Chi-squared, Wilcoxon, and Kruskal-Wallis tests will be used, as appropriate, to examine differences among novel therapeutic agent and PMR characteristics, including therapeutic area, agent type, orphan status, and PMR category. Analyses were performed using SAS version 9.4 (SAS Institute Inc.). All statistical tests were 2-tailed and used a type I error rate of 0.01 to account for multiple comparisons across 5 therapeutic agent and indication characteristics.

SUPPLEMENTARY CONTENT 1

Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved Between 2009 and 2012: a Cross-Sectional Evaluation

Joshua D Wallach; Alexander C Egilman; Sanket S Dhruva, Margaret E McCarthy;
Jennifer E Miller; Steven Woloshin; Lisa M Schwartz; Joseph S Ross

APPENDIX BOX 1. FDA Postmarketing Requirement Status Categories[1]	
Open Status Categories	
Pending	"The study/clinical trial 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)."
Ongoing	"The study/clinical trial is proceeding according to, or is ahead of, the original schedule. The FDA considers a study/clinical trial to be ongoing until a final report is submitted to the FDA, as long as the activities are proceeding according to the original 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/clinical trial should be categorized as *delayed*."
Delayed	"The progression of the study/clinical trial is behind the original schedule. Delays can occur in any phase of the study/clinical trial, including patient enrollment, analysis of results, or submission of the final report to the FDA. While the original schedule—not a revised schedule—serves as the basis for defining a study/clinical trial as delayed, each phase of the study/clinical trial 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."
Terminated	"The applicant ended the study/clinical trial before completion and has not yet submitted a final report to the FDA."
Submitted	"The applicant has concluded or terminated the study/clinical trial and has submitted a final report to the FDA, but FDA has not yet notified the applicant in writing that the requirement/commitment has been fulfilled or that the requirement/commitment has been released."
Closed Status Categories	
Fulfilled	"The applicant has submitted the final report for the requirement/commitment, and, upon review of the final report, FDA is satisfied that the applicant has met the terms of the requirement/commitment."
Released	"FDA has informed the applicant that it has been released from its requirement/commitment to conduct the postmarketing study/clinical trial because it is either no longer feasible or would no longer provide useful information."

APPENDIX BOX 2. Postmarking requirement examples
New prospective cohort studies, registries, and clinical trials
"A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy. Description of trial: This will be a Phase 3 multi-center, randomized clinical trial in patients with CTCL. The primary endpoint will be progression-free survival (PFS). Response rate will be a secondary endpoint. Prior to initiation of the Phase 3 trial, a Phase 1 trial will be conducted to determine the maximum tolerated dose (MTD) of the combination."
Complete or submit results from ongoing prospective cohort studies, registries, and clinical trials
"Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 1 (C0743T08) trial for a total of 5 years from initial enrollment unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through 5 years (even if treatment is not continued for this duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events."
New retrospective observational studies
"A retrospective cohort study using multiple existing observational databases to collect data from a 5-year period prior to the availability of denosumab. The study should identify women with postmenopausal osteoporosis and determine the occurrence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in each database in order to assess the background rates of those adverse events. The data obtained in this study will be used to inform the implementation of postmarketing requirement #2. The final protocol for this study was submitted on January 25, 2010."
New animal or "other" studies required
"A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Xeomin (incobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development."
Analyze/follow-up from observational studies, registries, or clinical trials (and other flexible requirements)[b]
"To characterize the safety of Iclusig™ (ponatinib), submit longer safety follow-up data of at least 12 months for all ongoing patients in the randomized controlled trial AP24534-12-301 that adequately isolates the effect of the drug."
Analyze/follow-up from an existing animal or "other" studies (and other flexible requirements)[b]
"To submit a final report for the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone)."

APPENDIX TABLE 1. Study Characteristics of Prospective Cohort Studies, Registries, and Clinical Trials Based on Postmarketing Requirement Descriptions

	No. (%)														
	Randomization			**Allocation**				**Comparator**				**At Least One Outcome Provided**		**Duration**	
Prospective Cohort Studies, Registries, and Clinical Trials	Randomized	Non-randomized	Unclear	Double Blind	Single Blind	Open label Blind	Unclear	Placebo	Active	None	Unclear	Yes	No	Provided	Unclear
Prospective cohort studies (n=5)	0 (0.0)	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)	0 (0.0)	3 (60.0)	0 (0.0)	2 (40.0)	0 (0.0)	5 (100.0)	0 (0.0)	0 (0.0)	5 (100.0)
Registries (n=19)	0 (0.0)	19 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)	5 (26.3)	0 (0.0)	13 (68.4)	1 (5.3)	14 (73.7)	5 (26.3)	5 (26.3)	14 (73.7)
Clinical Trials (n=110)	55 (50.0)	17 (15.5)	38 (34.5)	21 (19.1)	3 (2.7)	24 (21.8)	62 (56.4)	22 (20.0)	19 (17.3)	25 (22.7)	44 (40.0)	44 (40.0)	66 (60.0)	10 (9.1)	100 (90.9)
Total (n=134)	55 (41.0)	41 (30.6)	38 (28.4)	21 (15.7)	3 (2.2)	48 (35.8)	62 (46.3)	30 (22.4)	19 (14.2)	40 (29.9)	45 (33.6)	63 (47.0)	71 (53.0)	15 (11.2)	119 (88.8)

APPENDIX TABLE 2. Postmarketing Requirement Status Based on FDA's Postmarket and Commitment Database for New Drugs and Biologics Approved by the FDA Between 2009 and 2012

	Numbers based on current data, number based on old data[a]								
Postmarketing Requirements	**Status[b]**								**Total**
All (N = 437)	Pending	Ongoing	Delayed	Terminated	Submitted	Fulfilled	Released	Unclear	
New prospective cohort studies or trials (N = 119)	7, 7	37, 3	21, 2	0	5, 0	27	9	2	106, 14
Complete or submit results from prospective cohort studies, registries, and clinical trials (N = 15)	0, 2	0, 0	0, 0	0	0, 0	12	1	0	13, 2
New observational studies (N = 19)	2, 3	5, 2	1, 0	0	1, 0	1	4	0	14, 5
New animal or "other" studies (N = 219)	2, 41	8, 3	6, 2	0	5, 8	105	10	29	136, 83
New or analyze/follow-up from observational studies, registries, and trials (N = 47)	2, 9	8, 2	3, 1	1	2, 2	14	0	3	30, 17
New or analyze/follow-up from an existing animal or "other" studies (N = 17)	0, 4	0, 0	0, 2	0	0, 2	7	0	2	7, 10
Total separated	13, 66	58, 10	31,7	1	13, 12	166	24	36	306, 131
Total combined	79	68	38	1	25	166	24	36	437

[a] The second value represents the last available status for postmarketing requirements without a clear up-to-date status. Archived FDA Postmarketing Study and Clinical Trial Requirements and Commitments Database Files were used to determine the most recent status and date for each postmarketing requirement (e.g., "last available status: *Pending,* October 31, 2010).

[b] 50 postmarketing requirements were classified as fulfilled according to supplemental letters on Drugs@FDA and 106 had a status provided by the drug sponsor.

REFERENCES

1. U.S. Food and Drug Administration. Postmarketing Requirements and Commitments (FAQ). https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm. Accessed 5 Dec 2017.