Timeliness of Postmarket Studies for New Pharmaceuticals Approved Between 2009 and 2012: a Cross-Sectional Analysis

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INTRODUCTION

Over the past decade, the US FDA's framework for evaluating new drugs has shifted from a predominantly premarket to an increasingly "lifecycle" evaluation process, where benefits and risks are evaluated before and after market approval.[1] In order to resolve remaining uncertainties at the time of premarket approval, such as whether a drug conditionally approved on a surrogate marker improves patient outcomes, many drugs receive postmarketing requirements (PMRs)—FDA-imposed studies that manufacturers must conduct after approval. To avoid delays translating these findings into practice, manufacturers need to complete PMRs on time and FDA should provide reasonable time frames for completion. However, concerns have been raised about manufacturers' lack of adherence to and FDA's lack of enforcement of PMR deadlines.[2] Furthermore, nearly one quarter of PMR results are either not reported on ClinicalTrials.gov or published in the peer-reviewed literature.[3, 4] Therefore, our objective was to characterize the timeliness of PMR studies, comparing FDA-established timeliness milestones with expected completion times outlined on ClinicalTrials.gov.

METHODS

As previously described,[4] we identified all PMRs from the approval letters in the Drugs@FDA database for new drugs and biologics approved between 2009 and 2012. Approval letters include descriptions of PMRs and identify the regulatory authorities under which they are required (Accelerated Approval (AA), Pediatric Research Equity Act (PREA), or FDA Amendments Act (FDAAA)) (Table 1). We limited our sample to clinical PMR studies examining drug safety or efficacy, including new prospective cohort studies, clinical trials, and registries.[4]

We collected FDA approval dates for each drug and milestone dates established by FDA for each PMR study, including final protocol submission, trial completion, and final report submission. We searched ClinicalTrials.gov for registration records to identify primary outcomes and the timing of their measurement (e.g., primary outcome ascertainment: change from baseline to day 56 in syndrome scale), as a proxy for expected study duration. Using FDA milestone dates, we determined time from first approval to protocol submission, time from protocol submission to study completion, and time for primary outcome ascertainment. Analyses were performed using R (v.3.2.3).

FINDINGS

Between 2009 and 2012, FDA approved 110 new drugs and biologics: 66 for 73 indications had at least one clinical PMR study. The median number of clinical PMR studies per approval was 1 (interquartile range, 1–2; max, 5). Among a total sample of 119 clinical PMR studies, 95 (80%) were clinical trials, 53 (56%) of which were pediatric trials required under the PREA authority (Table 2).

Median time from drug approval to protocol submission was longer for clinical trials required under PREA than under FDAAA and AA authorities: 15 (7–37) vs 4 (3–6) and 3 (2–9) months, respectively (Table 2).

Median PMR study durations set by FDA (protocol submission to study completion) for clinical trials required under PREA, FDAAA, and AA were substantially longer than median time required for primary outcome ascertain-

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Table 1 The US Food and Drug Administration's Postmarketing Requirement Authorities

Authority (year implemented)	Purpose and requirement	Drug/indication(s)	Postmarketing requirement example	Uncertainties addressed by postmarketing requirement
Accelerated Approval pathway (1992)	To expedite the approval of certain drugs that treat serious diseases and that fill an unmet medical need, FDA approval can be made on the basis of trials with surrogate endpoints "reasonably likely" to predict clinical benefit. FDA then has the authority to require postmarket studies or confirmatory clinical trials.[4]	Bedaquiline Fumarate/MDR-TB	"Conduct a confirmatory randomized double blind placebo controlled multicenter Phase 3 trial in subjects with sputum smear-positive pulmonary multidrug-resistant tuberculosis (MDR-TB). This trial should assess long-term outcomes of failure or relapse or death at least 6 months after all MDR-TB treatment is completed"	FDA approval was based on two small randomized-controlled trials evaluating surrogate microbiological markers of treatment response. A confirmatory clinical trial evaluating a clinical outcome is necessary.
Pediatric Research Equity Act (*PREA*) (2003)	To provide pediatric use information in product labeling for drugs developed for indications that occur in both adult and pediatric patients, FDA can approve drugs for use in adults without corresponding studies for the same indication in the relevant pediatric population.[4] However, FDA can include deferred pediatric studies or clinical trials as postmarketing requirements.	Ceftaroline Fosamil/ABSSSI and Community Acquired Bacterial Pneumonia	"Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with ABSSSI including patients with infection suspected or demonstrated to be caused by MRSA. Pediatric patients under 17 years of age with ABSSSI must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil)"	FDA approval was granted for use in adults. Under PREA, all application for new indications, dosage forms, dosing regimens, routes of administration, and indications are required to contain effectiveness and safety assessments of the product for claimed indication in pediatric populations, unless they are inapplicable, deferred, or waived. Ceftaroline Fosamil was approved with a deferred submission.
Food and Drug Administration Amendments Act (*FDAAA*) (2007)	To provide additional information for novel drugs, 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.	Tocilizumab/ Rheumatoid arthritis	"A randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g., stroke, non-fatal MI, cardiovascular death"	FDA approval was based on 5 multinational phase 3 clinical trials with > 4000 patients. However, safety concerns were reported in tocilizumab-treated patients.

FDA, Food and Drug Administration; MDR-TB, multidrug-resistant tuberculosis; ABSSSI, acute bacterial skin and structure infection; MRSA, methicillin-resistant Staphylococcus aureus; MI, myocardial infarction; PREA, Pediatric Research Equity Act. Our sample did not contain any clinical trials issued under the Animal Efficacy Rule (AER) (2002). Under AER, postmarketing requirements may be issued for certain drugs approved without human efficacy studies and field trials when they are not ethical and feasible

ment: 38 (29–51) vs 3 (1–6), 53 (42–67) vs 12 (3–48), and 72 (56–80) vs 46 (14–60) months, respectively.

DISCUSSION

Across PMR authorities, median times permitted by FDA for manufacturers to submit protocols for PMR clinical trials ranged from 3 to 15 months, while median times allowed for study completion after protocol submission were approximately 2–13-fold longer than that required for primary outcome ascertainment. PREA trials had the longest protocol submission milestones, likely reflecting FDA's policy of deferring studies in children until safety information from other studies is available.[5] AA drugs, which receive provisional approval based on surrogate markers, had the longest PMR trial completion milestones, approximately 2 years longer than the time required for primary outcome ascertainment.

While limited to a relatively small sample of clinical PMR studies with trial information determined from publicly available data, our results suggest that FDA and manufacturers should consider strategies to shorten times allotted for PMR milestones. If FDA currently does not have the capacity to provide detailed oversight during PMR protocol development, additional resources may be necessary to strengthen postmarket evidence generation such as improvements in FDA's data management system.[6] FDA and manufacturers could work to identify PMRs earlier in the approval process, potentially shortening the time from approval to protocol submission and study initiation. Shorter milestones may

Table 2 Timing Between FDA Milestones for PMR Studies of New Drugs and Biologics Approved Between 2009 and 2012

PMR	Studies (no.)	Timing between FDA milestones Months, median (IQR) [range]				Timing of primary outcome ascertainment Months, median (IQR) [range]*
		Approval to protocol submission	Protocol submission to study completion	Study completion to final report submission	Approval to final report submission	Primary outcome
FDAAA						
Clinical trials	35	4 (3–6) [− 59–41]†	53 (42–67) [5–104]	6 (5–9) [− 11–36]‡	64 (44–80) [9–145]	12 (3–48) [0–99]
Prospective cohort studies	5	4 (4–5) [0–10]	53 (50–111) [28–163]	6 (5–7) [2–8]	62 (56–122) [40–176]	36 (15–60) [12–120]
Registries	19	5 (3–9) [− 1–13] †	86 (66–136) [6–195]‡	8 (6–12) [6–120]‡	123 (87–146) [57–221]‡	21 (12–72) [1–180]
Pediatric Research Equity Act§						
Clinical trials	53	15 (7–37) [− 2–73]†‡	38 (29–51) [6–102]‡	6 (6–8) [2–57]‡	66 (55–87) [1–170]	3 (1–6) [0–24]
Accelerated approval§						
Clinical trials	7	3 (2–9) [− 30–18]†	72 (56–80) [47–98]	6 (6–6) [5–7]	93 (64–95) [22–110]	46 (14–60) [12–84]

FDA, Food and Drug Administration; FDAAA, Food and Drug Administration Amendments Act; IQR, interquartile range; no., number; PMR, postmarketing requirement; range, full range

**Primary endpoint duration based on PMR descriptions or corresponding ClinicalTrials.gov data. Number of PMR studies excluded due to unavailable primary outcome duration: 4 FDAAA clinical trials, 6 registries; 20 PREA, 1 AA*

†Protocol submission date before drug approval date: 2 FDAAA, 1 PREA, 1 AA, leading to negative duration

‡Number of PMR studies excluded due to unavailable study completion dates (1 FDAAA, 3 PREA), final report submission dates (1 FDAAA), protocol submission dates (3 PREA)

§During this period, the eligible postmarket requirements under PREA and AA were only clinical trials

help ensure more timely resolution of the medical product uncertainties that remain at the time of approval, thereby improving clinical care decision-making and reducing the amount of time that drugs are available without long-term safety and/or efficacy data.

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Compliance with Ethical Standards:

***Conflict of Interest:** In the past 36 months, Dr. Wallach received research support through the Meta Research Innovation Center at Stanford (METRICS) from the Laura and John Arnold Foundation. Dr. Ross has received research support through Yale University 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 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; from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting (HHSM-500-2013-13018I); from the Agency for Healthcare Research and Quality (R01HS022882); from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) (R01HS025164); and from the Laura and John Arnold Foundation to establish the Good Pharma Scorecard at Bioethics International; in addition, Dr. Ross receives an honoraria as compensation for his role as an Associate Editor of JAMA Internal Medicine. Drs. Schwartz and Woloshin were cofounders of Informulary, Inc., a company that provided data on the benefits, harms, and uncertainties of prescription drugs. The company has ceased operations. Drs. Schwartz and Woloshin report personal fees from Ross Feller Case, LLP, for serving as medical experts in testosterone litigation. All remaining authors declare that they do not have a conflict of interest.

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