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SYSTEMATIC REVIEW

New Drug Postmarketing Requirements and Commitments in the US: A Systematic Review of the Evidence

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Abstract

Introduction After the approval of a new drug, the Food and Drug Administration (FDA) may issue postmarketing requirements (PMRs), studies that the law requires manufacturers to conduct for drugs approved under certain conditions, and postmarketing commitments (PMCs), studies that the FDA and manufacturers agree should be conducted as a condition of approval.

Objective With regulators' increasing reliance on gathering important evidence after initial product approval, we sought to assess the track record of PMRs and PMCs by synthesizing information about postmarketing study completion rates, timeliness, study types, and results reporting.

Methods A systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted. Studies published in academic journals or government reports that reported original data about the characteristics of PMRs or PMCs were included. Studies of post-approval trial mandates issued by regulators outside the USA were excluded, as were those that addressed post-approval research without mentioning either PMCs or PMRs or a specific approval pathway associated with statutorily required PMRs. Two investigators independently screened and extracted data from studies and reports. Data sources included the *Federal Register* from 2003 to 2020, FDA backlog reviews from 2008 to 2020, PubMed from January 2006 to April 2021, and the US Government Accountability Office (GAO) database for reports from January 2006 to April 2021. PMR/PMC characteristics (e.g., completion rates, timeliness, results reporting, outcomes) were not meta-analyzed due to the heterogeneity in study designs.

Results Twenty-seven peer-reviewed articles from PubMed, five GAO reports, 17 annual *Federal Register* notices, and 12 annual backlog reviews were included. Among the 27 studies, 13 reviewed PMRs and PMCs, one reviewed only PMCs, and 13 reviewed only PMRs. A majority of new drugs were approved with at least one PMR or PMC. PMCs were completed at higher rates than PMRs, although delays were common and neither was found to be completed more than two-thirds of the time. Over two-thirds of PMRs and PMCs reported their findings in publications and trial registries. Over half of PMCs and PMRs produced novel information for clinical practice or leading to regulatory action, such as confirmation of benefit or a labeling change.

Conclusion PMRs and PMCs are common for new drugs and can lead to worthwhile outcomes, but are often delayed or incomplete. Greater attention is needed to timely completion, improving transparency of findings, and ensuring that PMRs and PMCs produce optimally useful information for prescribers and patients.

1 Introduction

The Food and Drug Administration (FDA) approves drugs and biologics based on results from one or more pivotal clinical trials [1, 2], but approved drugs often require monitoring and testing after approval to clarify aspects of their effectiveness and safety [3, 4]. Post-approval testing is important because pre-approval trials inevitably have limitations, such as excluding certain patient populations (like children or elderly patients) or lasting for a few months for a drug that is expected to be taken for many years [5]. In addition, when a drug is approved based on a surrogate marker rather than a demonstrated clinical benefit, it is necessary

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Key Points

Ensuring the completion and the clinical usefulness of post-approval studies remain important ongoing issues

Literature evaluating post-approval studies shows that postmarketing requirements (PMRs) and postmarketing commitments (PMCs) are not being completed on time

The utility and relevance of data from PMRs and PMCs varies based on the type of requirement, suggesting that policy reforms may consider targeting specific legislative authorities of PMRs and PMCs

to confirm whether the expected benefits occur once it is in widespread use.

When the FDA believes that more data on efficacy or safety is required following approval, it can request manufacturers collect such information through two regulatory categories: postmarketing commitments (PMCs) and postmarketing requirements (PMRs) [6]. In contrast to other forms of pharmacovigilance (such as the FDA's Adverse Event Reporting System) that can provide greater insight about the safety of a product after approval through postmarketing surveillance, PMRs/PMCs answer particular questions about a product's safety or efficacy through studies such as clinical trials or observational studies. PMRs/PMCs include pharmacokinetics/pharmacodynamics (PK/PD) studies or chemistry, manufacturing, and control (CMC) studies. PMCs are studies that the FDA and manufacturers agree should be conducted as a new drug is being approved, but manufacturers are not legally bound to complete the studies [7]. By contrast, PMRs are studies that manufacturers must conduct for drugs approved under certain conditions. There are three major legislative authorities under which PMRs may be issued: studies of a drug in children under the *Pediatric Research Equity Act* (PREA) to address safety and efficacy in pediatric populations [8], confirmatory studies for drugs approved based on effects on unvalidated surrogate measures via the Accelerated Approval program [9, 10], and studies organized under Sect. 505(o)(3) to obtain more information about a serious risk that may be associated with a drug [11]. PMRs are also required under the FDA's 2002 Animal Rule, but only about 16 drugs have been approved under this program since its inception. While all intend to produce additional evidence for drugs after approval, each of these PMR legislative authorities has a different policy aim. For example, evaluating the performance of PMRs under the PREA can provide an understanding of how carefully medical products are being tested in children, while assessing PMRs under Accelerated Approval would provide insight into how diligently clinical benefit is measured after initial drug approval via that program. Evaluating PMRs under Sect. 505(o)(3) provides an understanding of how well safety risks are studied once a drug is marketed.

In recent years, new drugs have been subject to less extensive pre-approval testing, shifting more of the initial evidence generation for these products to after approval [12–14]. However, the FDA has considerably less influence over manufacturers after a product is approved. As a result, PMCs and PMRs have frequently been criticized for being left incomplete or delayed. In 2007, the *FDA Amendments Act* (FDAAA) gave the FDA more authority in this area, such as the use of civil monetary penalties [under section 303(f)(4)(A) of the act], to ensure that manufacturers complete the PMCs and PMRs in a timely fashion [11, 15]. Through FDAAA, Congress required that the FDA publish annual notices in the *Federal Register* concerning the status of PMRs and PMCs (see Box) [16]. The law also required the FDA to annually review the backlog of pre-FDAAA PMRs and PMCs [11].

Previous analyses characterizing PMRs and PMCs have been focused on specific study samples restricted to certain time frames, drug categories (e.g., only cancer drugs), or certain subsets of PMRs, such as Accelerated Approval. As a result, conclusions from previous investigations may be limited to the contexts studied by each analysis. We sought to synthesize the available evidence to understand how often all postmarketing studies are completed, whether they are completed in a timely fashion, to what extent results from postmarketing studies are publicly disseminated, and how often postmarketing studies produce clinically useful information. We conducted a systematic review of information since 2006 that evaluated postmarketing study completion rates, timeliness, results reporting, and study outcomes.

2 Methods

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Fig. 1), we performed a PubMed search on April 2, 2021, for articles on this topic since January 2006 (Supplemental Table 1, see the electronic supplementary material) using categories that included PMRs or PMCs and glossary terms attributable to the FDA, supplemented with a review of the US Government Accountability Office (GAO) database. We then manually mined the references of our sample of articles to add any records missed. We additionally extracted annual *Federal Register* notices from 2003 to 2020 and backlog reviews from 2008 to 2020 [17].

Definitions of key terms. Legend: In a 2011 guidance document, the Food and Drug Administration (FDA) clarified the terminology of PMRs and PMCs to distinguish required studies versus agreed-upon studies. See FDA. Guidance for industry: postmarketing studies and clinical trials—implementation of Section 505(o)(3) of the FDCA. April 2011

Postmarketing Commitment (PMC): A study that a manufacturer has agreed upon conducting after approval of a product.

Postmarketing Requirement (PMR): A study that a manufacturer is required to conduct after approval of a product.

Surrogate Measure: An intermediary endpoint (e.g., progression-free survival or time to tumor progression) expected to predict a clinical outcome, such as mortality.

PMR/PMC Status: A PMR/PMC would be classified as "pending" if it had not been initiated, "ongoing" if it was proceeding according to its original schedule, "delayed" if it was proceeding behind the original schedule, "submitted" if a final report had been submitted to the FDA, and "terminated" if it was ended before completion but a final report was not yet submitted. A PMR/PMC would be classified as "fulfilled" if the final report was submitted. A PMR/PMC would be classified as "released" if the FDA determined that it no longer provided useful information or was not feasible to conduct.

We included English-language studies published in peer-reviewed journals or government reports, and excluded publications lacking original data. Included studies and government reports reported empirical data about the characteristics of all FDA PMRs or PMCs for drugs or biologics. We excluded studies or government reports of any post-approval trial mandates issued by non-US regulators and studies or government reports of medical devices. We did not consider studies or government reports that addressed post-approval research without explicitly mentioning either PMCs or PMRs, or a specific PMR authority, such as Accelerated Approval. Two investigators (OM and BLB) independently screened all citations and articles first at the title and abstract level, then evaluated all potentially eligible records at the full text level. Discrepancies were resolved by a third investigator (ASK).

For each article, we recorded the methodology, general conclusions, number of products, and number of postmarketing studies. We also extracted data on PMR/PMC study completion rates, timeliness, results reporting, and outcomes. Two investigators (OM and BLB) independently extracted data from included studies and government reports, and discrepancies were resolved by discussion. Authors were not contacted for additional information. Results were summarized with a qualitative synthesis of the data by two investigators (OM, ASK) and reviewed by all other investigators. Given the heterogeneity of the data, a quantitative synthesis was not possible.

We used a multi-tiered approach to organize the various studies and government reports included in our review. We first synthesized findings across the FDA documents (i.e., annual *Federal Register* notices) as well as published studies evaluating these same FDA documents. We then turned our attention to the published studies identified in the literature search. We organized these published studies according to the type of postmarketing studies they considered: studies of all post-approval studies, studies addressing only postmarketing commitments, and studies addressing only postmarketing requirements. Finally, we highlighted trends across key postmarketing study characteristics (i.e., completion rates, timeliness, results reporting, and outcomes) without separating across postmarketing study types.

3 Results

The PubMed search returned 151 articles and the GAO search returned 154 potential reports for inclusion, from which 243 were excluded during initial screening based on the title and abstract. Sixty-two published studies and reports were reviewed at the full-text level, from which 27 published studies and five government reports were identified as relevant (Fig. 1). There were 17 annual *Federal Register* notices and 12 annual backlog reviews extracted from the FDA's website [17].

3.1 FDA Documents

3.1.1 Annual Federal Register Notices

In the FDA's 2020 report, 334 New Drug Application (NDA) and Biologics License Application (BLA) applicants had open PMRs/PMCs as of September 30, 2019 (i.e., pending, ongoing, delayed, submitted, or terminated; see Box). Of the 1383 PMRs and 357 PMCs that had an open status, over three-quarters ($N = 1355$) were reported as being "on-schedule." Approximately three-quarters ($N = 213$) of the 224 PMRs and 66 PMCs that had a closed status (i.e., fulfilled or released) were reported as being fulfilled.

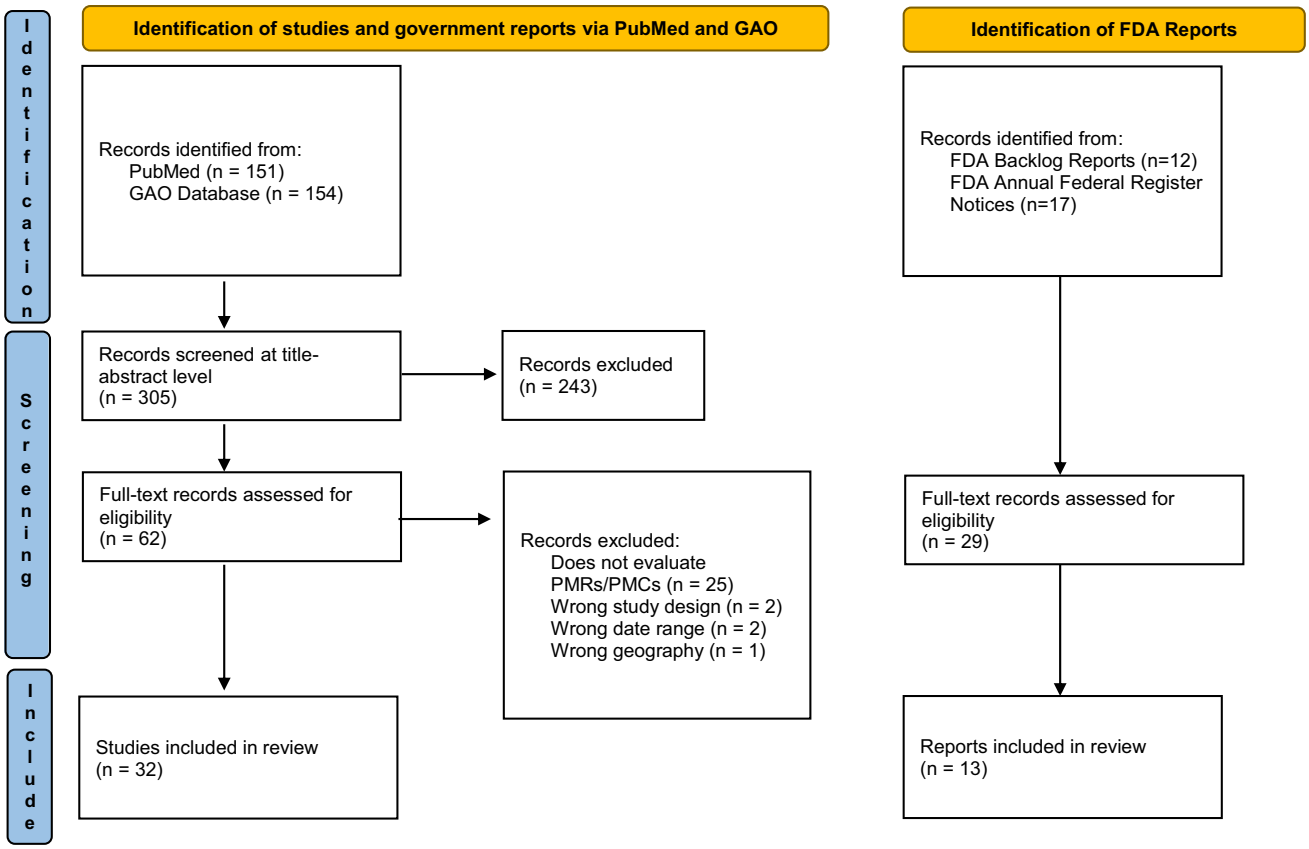

Fig. 1 Study flowchart. *FDA* Food and Drug Administration, *GAO* Government Accountability Office, *PMC* postmarketing commitment, *PMR* postmarketing requirement

Three studies from the literature review analyzed time trends from these annual reports [18–20]. Fain et al. focused on PMRs and PMCs open (studies that were ongoing and not yet complete) in years 2007–2011 and then followed them until 2012, observing that the total number of pending studies had decreased during the time period, though over 40% had still not been started by 2012. The proportion of concluded studies with commitments fulfilled increased during that time period and the proportion of delayed studies increased [18]. Woloshin et al. reviewed PMRs/PMCs issued in 2009–2010, and followed until 2015 [19]. They found that while approximately half ($N = 333$) of postmarketing studies were completed, one-quarter ($N = 156$) were classified as delayed or ongoing and one-fifth ($N = 125$) were not yet started. Even for the portion of postmarketing studies that were on schedule, Woloshin et al. concluded that the FDA-specified study schedules were longer than necessary. In a 2020 article, Dauner et al. found that 46% of PMRs/PMCs from 2013–2014 were completed, while 30% were delayed or ongoing and 24% were not started [20].

3.2 Published Studies of Postmarketing Requirements and Commitments

Among the 27 studies, 13 reviewed PMRs and PMCs, one reviewed only PMCs, and 13 reviewed only PMRs. Of the latter, two considered all PMRs generally, eight focused on PMRs issued under Accelerated Approval, and three on PMRs issued under the PREA.

3.2.1 Studies of PMRs and PMCs

Thirteen studies evaluated both main types of post-approval studies requested or required by the FDA [18–30]. For example, in 2014, Moore et al. reviewed postmarketing studies for new drugs approved in 2008 [22], the first full-year cohort of therapeutics after the FDAAA. They found that of 85 PMRs and PMCs for 19 of 20 drugs approved that year, 31% had been fulfilled by January 2013, with 71% completed or submitted on schedule. Postmarketing studies for drugs approved via expedited review (40%) were fulfilled at a higher rate than those for drugs approved via standard review (15%).

In 2021, Skydel et al. considered all new therapeutics approved between 2009 and 2018 [21]. They found that 91% of new therapeutics were approved with at least one PMR or PMC (median 5). Among their sample of 1978 PMRs and PMCs, 38% were designed to produce safety or efficacy evidence and 62% were non-clinical (e.g., PK/PD or CMC studies). One-quarter ($N = 184$) of clinical studies explored unapproved indications.

FDA investigators published an internal review [23], finding that of 288 fulfilled PMRs and PMCs for new drugs approved in 2009–2013, 64% were published in the scientific literature or on ClinicalTrials.gov by July 2016.

Seven studies reviewed PMRs and PMCs for specific types of products [24–30]. Hyogo et al. reviewed PMRs and PMCs for oncology products approved in 2008–2015, finding a median of 4.0 (interquartile range [IQR] 2.0–6.0) per product [27]. Hyogo et al. found that products approved based on nonrandomized trials or small pivotal trial populations were more likely to later undergo clinical safety studies or confirmatory studies. Lu et al. reviewed 11 PMRs and PMCs related to dose optimization for oncology indications (2010–2015) [25], finding that PMRs and PMCs may be issued to evaluate a higher dose of a product if there appeared to be a trend toward greater efficacy related to increased exposure without added safety risks. PMRs and PMCs were also issued to evaluate a lower dose if that appeared to reduce risks without compromising efficacy [25]. Hung et al. examined PMRs and PMCs for new biosimilars, finding that the PMRs were related to pediatric studies, while the PMCs were typically related to analytical testing, such as identifying similarity between primary structure, bioactivity, and chemical purity [26]. Moneer et al. investigated the characteristics of PMRs and PMCs for new vaccines (2006–2020), finding a median of four PMCs or PMRs, with 41% of PMRs and 54% of PMCs fulfilled, at a median of 50 months [29].

3.3 Studies Addressing Only PMCs

In 2019, Wallach et al. investigated the characteristics of PMCs for new drugs and biologics approved in 2009–2012 [31]. Among 331 PMCs issued for 61 new drugs and biologics, 82% were for "other studies" (mostly CMC studies or animal studies), while only 10% of PMCs required new clinical studies. While 41% of new clinical trial PMCs were classified as fulfilled, half ($N = 14$) were published. The median time from approval to reporting results or publication was 65 months (IQR 47–81).

3.3.1 Studies Addressing Only PMRs

Two studies conducted examined PMRs (2009–2012) [32, 33]. Wallach et al. reported on 437 PMRs issued for 97 new drugs and biologics, finding about one-third (31%) were "prospective cohort studies, registries, and clinical trials," including trials evaluating safety and efficacy. Half (50%) were "new animal or 'other' studies," a category that included PK and PD studies, dosing studies, and other studies investigating nonclinical endpoints [32]. Among the 134 prospective cohort studies, registries, and clinical trials, 33% were submitted/fulfilled by November 2017, allowing at least 4 years for completion of postmarketing studies. In a follow-up study, the authors focused on the 119 PMRs evaluating drug safety or efficacy [33]. The median time from approval to protocol submission for PMRs under the PREA was 15 months, 4 months for PMRs under Sect. 505(o)(3), and 3 months under Accelerated Approval. The median time between protocol submission to study completion for PMRs was 38 months under the PREA, 53 months under Sect. 505(o)(3), and 72 months under Accelerated Approval.

Eight studies considered PMRs for Accelerated Approval drugs [34–41]. In a study of the Accelerated Approval program for oncology drugs (1992–2017), FDA investigators Beaver et al. found 55% of the indications in their sample had fulfilled their PMRs, 5% of studies were withdrawn, and 40% were incomplete or had not yet verified clinical benefit by 2017 [35]. Median time from Accelerated Approval to fulfillment was 3.4 years (range 0.5–12.6 years). One year later, Gyawali et al. re-reviewed the same sample of studies, finding that 39 (67%) of 58 trials that confirmed clinical benefit had done so based on surrogate measures rather than clinical outcomes [36]. In 2017, Naci et al. investigated 38 post-approval trials for 22 new drugs granted Accelerated Approval (2009–2013), finding that about one-half ($N = 19$) of confirmatory trials were completed by April 2017, 29% were underway and on schedule, and 16% were reported as delayed by more than 12 months, with a range of 1.3–5.3 years from Accelerated Approval to fulfillment [37].

Three studies assessed PMRs subject to the PREA [42–44]. Hwang et al. investigated the characteristics of 222 PMRs required under the PREA for 114 new drugs and new indications (2007–2014) [42]. A majority of studies primarily tested efficacy (60%), while 25% studied safety, and 15% PK/PD. By December 2017, 34% (75/222) of studies were completed, and efficacy studies were completed at the lowest rate (29%). Bourgeois and Kesselheim reviewed 770 labeling changes for 620 products attributed to the PREA (1998–2018), with 187 of 253 (73.9%) labeling changes between 2014 and 2018 attributed solely to the PREA and most expanding indications from adults to pediatric populations [43]. Winiecki et al. reviewed pediatric trial registries in the April 2014 version of the FDA Postmarketing Requirements and Commitments database, finding ten of 24 studies were "successful" (results published or submitted to the FDA), four were unsuccessful, and ten were not evaluable [44].

3.4 Trends in Completion Rates, Timeliness, Results Reporting, and Outcomes

3.4.1 Completion Rates

Completion rates differed for PMRs versus PMCs (Table 1). In two different studies, Wallach et al. found that for PMCs issued for new products between 2009 and 2012 and followed until July 2018, 41% were fulfilled [31], while 33% of PMRs from around the same time period for prospective cohort studies, registries, and clinical trials were fulfilled (followed only through October 2017) [32]. Completion rates varied across subtypes of PMRs. Beaver et al. found that 55% of cancer drugs receiving Accelerated Approval had fulfilled their PMRs (issued between December 1992 and May 2017, followed until May 2017) [35], while Hwang et al. showed that 34% of pediatric studies required under the PREA (issued between 2007 and 2014, followed until December 2017) had been completed [42].

3.4.2 Timeliness

The median time between product approval and postmarketing study completion was investigated in several studies (Table 2), with Moneer et al. finding this to be 50 months for 60% of new vaccine PMRs and PMCs [29]. Completion times for Accelerated Approval PMRs ranged widely. Beaver et al. found that the median time from Accelerated Approval to fulfillment was 3.4 years (range 0.5–12.6 years) over the first 25 years of the Accelerated Approval program [35], while Naci et al.—examining a smaller but more recent sample—showed that the time from Accelerated Approval to study fulfillment for 42% of studies fulfilling their requirements was 1.3–5.3 years [37].

3.4.3 Results Reporting

Not all results of PMCs and PMRs were reported in either the literature or ClinicalTrials.gov (Table 3). Cruz et al. found that 64% of reportable postmarketing studies published results [23], with results reporting varying by the legislative authority (e.g., Accelerated Approval, the PREA). Naci et al. found that Accelerated Approval PMRs reported results 90% of the time [37], compared to findings from Hwang et al. showing that results were reported for 76% of completed pediatric studies under the PREA [42].

3.4.4 Outcomes

More than half of PMCs and PMRs produced novel clinical information, such as confirmation of benefit or information that led to a labeling change due to safety, efficacy, or other reasons (Table 4). Guinn et al. showed that 55% of PMRs and PMCs in their sample of products undergoing immunogenicity assessments led to related labeling changes, while the other 45% maintained their original labeling information [30]. Several studies addressed how often drugs receiving Accelerated Approval verified clinical benefit, with Gyawali et al. showing 62% of drugs in their sample replicated a positive outcome, but often using the same surrogate measure; 9% did not confirm any benefit [36]. Johnson et al. described three drugs receiving Accelerated Approval that later did not show clinical benefit in confirmatory trials [34].

4 Discussion

Studies and government reports evaluating execution of PMRs and PMCs since the FDAAA provide details on completion rates of postmarketing studies, time required for study completion, transparency in results reporting, and postmarketing study outcomes. New policy approaches may be needed to maximize timely completion and the clinical usefulness of post-approval studies.

PMCs have generally been completed at higher rates than PMRs. This might seem paradoxical, since PMCs are agreed-upon conditions under less strict terms than PMRs, which are required by law. However, manufacturers may be more likely to complete PMCs because they had more flexibility to set the terms of the study. PMCs may include simpler postmarketing studies, such as long-term follow-up of an existing study or submitting final datasets for completed clinical trials, while PMRs more often involve new clinical trials. PMRs under Accelerated Approval were completed at higher rates than PMRs under the PREA or under Sect. 505(o)(3). Beyond the difficulties post-approval studies face recruiting patients, it can be challenging to enroll children in research studies due to lower rates of disease burden in children as well as the increased requirements for receiving consent in children [45, 46]. Additionally, PMRs issued under Sect. 505(o)(3) apply to late-arising safety questions, and so may be more difficult to organize as manufacturers would have to design studies to fulfill these requirements partway through the clinical development of a drug. Manufacturers usually position their products to receive Accelerated Approval earlier in development, and the FDA now encourages manufacturers to have PMRs underway at the time of approval.

Our analysis of the FDA's backlog reports for pre-FDAAA PMRs and PMCs (i.e., those that were not fulfilled or released by September 27, 2007, when the FDAAA was enacted) was reassuring [17]. The most recent backlog review from 2020 reported that by the end of 2019, 96% of studies (1563/1636) had a closed status (fulfilled or released). While ensuring completion of PMRs/PMCs is

Table 1 Studies highlighting PMC and PMR completion rates

Study	Sample description	Key findings
Reviews of postmarketing requirements and commitments		
Guinn 2021 [1]	126 PMRs and PMCs for 56 products with immunogenicity assessments in their labeling approved 2009–2018	52% of products had at least one PMR/PMC fulfilled
Moneer 2021 [2]	128 PMRs and PMCs for 35 new vaccines approved 2006–2020	41% studies required under PMRs fulfilled. 54% studies required under PMCs fulfilled
Dauner 2020 [3]	PMRs and PMCs opened in 2011, 2012, 2013, and 2014	37% of PMRs open, 7% pending, and 12% delayed. 28% of PMCs open, 3% pending, and 5% delayed
Hyogo 2018 [4]	264 PMRs and PMCs for 54 oncology products approved 2008–2015	50% of Accelerated Approval products had completed confirmatory trials; 50% ongoing, pending, or delayed
Woloshin 2017 [5]	614 PMRs and PMCs opened 2009–2010	25% of studies delayed or ongoing, 54% completed, and 20% not yet started. Of the incomplete studies, 16% ongoing and on schedule, 5% on schedule but pending, and 15% released
Moore 2014 [6]	85 PMRs and PMCs for 19 new drugs approved in 2008	31% of studies fulfilled overall, with 40% ($N=19$) fulfilled for drugs approved under expedited review and 15% ($N=7$) fulfilled for drugs approved under standard review
Fain 2013 [7]	PMRs and PMCs for all new drugs and biologics between 2007 and 2011	57% of studies pending in 2007, while 44% of studies pending in 2011. 7% of studies fulfilled in 2007, vs. 13% in 2011. 7% of studies delayed in 2007, vs. 14% in 2011
Reviews of postmarketing commitments only		
Wallach *BMC* 2019 [8]	331 PMCs (33 PMCs for clinical trials; 27 PMCs subject to 506B reporting requirements) for 61 new drugs and biologics approved between 2009 and 2012	41% of PMCs for clinical trials fulfilled
Reviews of postmarketing requirements only		
Wallach *BMJ* 2018 [9]	437 PMRs (134 PMRs for postmarket prospective cohort studies, registries, and clinical trials) for 97 new drugs and biologics approved between 2009 and 2012	38% of PMRs fulfilled. 33% of PMRs for postmarket prospective cohort studies, registries, and clinical trials submitted or fulfilled
Chen 2019 [10]	53 confirmatory studies for 53 cancer drugs approved based on the surrogate endpoint of response rate receiving Accelerated Approval 2006–2018	55% ($N=29$) of authorizations had been converted to regular approval
Gyawali 2019 [11]	93 confirmatory studies for 64 cancer drugs granted Accelerated Approval Dec 11, 1992–May 31, 2017	64% of studies completed, 5% withdrawn, 10% ongoing, 11% pending, 5% delayed, 1% terminated, and 1% released
Beaver 2018 [12]	Confirmatory studies for 64 cancer drugs spanning 93 indications granted Accelerated Approval Dec 11, 1992–May 31, 2017	55% of drugs had fulfilled PMRs and verified clinical benefit, 40% had incomplete PMRs or not yet verified benefit, and 5% had withdrawn PMRs
Zettler 2018 [13]	34 clinical PMRs for 17 oncology drugs receiving Accelerated Approval 2011–2016	44% of PMRs completed, 41% ongoing, 6% terminated, and 9% pending
Naci 2017 [14]	38 PMRs required under Accelerated Approval for 22 new drugs approved 2009–2013	50% of PMRs completed, 16% delayed by over 12 months, 29% underway as planned, and 5% terminated
Gaddipati 2012 [15]	PMRs for 19 rare cancer drugs spanning 24 indications approved Dec 1987–May 2011	46% of indications had completed PMRs

Table 1 (continued)

Study	Sample description	Key findings
Johnson 2011 [16]	PMRs for 35 cancer drugs spanning 47 indications under Accelerated Approval approved Dec 11, 1992–July 1, 2010	55% of indications had been converted to regular approval. Of the 21 that had not yet been converted, 3 failed to show clinical benefit (subsequently withdrawn or restricted), 14 had not completed confirmatory trials, and 4 confirmatory trials under FDA review
Hwang 2019 [17]	222 PMRs required under PREA for 114 new drugs and new indications approved between 2007 and 2014	34% of studies completed. 2% of studies completed 1 year after approval, 7% completed 2 years after approval, and 27% completed 5 years after approval
Winiecki 2016 [18]	24 pediatric registries included in the April 2014 version of the FDA Postmarketing Requirements and Commitments database	16% of registries delayed/incomplete

still an ongoing goal, completing the backlog of previously outstanding studies before 2007 has largely been achieved.

Studies and government reports evaluating timeliness repeatedly found delays in some postmarketing studies. Two analyses further suggested that the FDA-issued timelines for study completion may overestimate the length of time a study would actually require to be completed; that is, not only are studies failing to meet their deadlines, those deadlines may already be too lenient [19, 33]. Stricter enforcement of post-approval study requirements, as some have proposed, therefore must guard against the possibility that it would lead to regulators setting even longer timelines. Doing so would give the appearance of increased rates of timely completion without necessarily accelerating the availability of the clinical information needed from the studies. Delays in study completion may not necessarily be regulatory failures. Postmarketing studies can be delayed for valid reasons, including slow recruitment for clinical trials or changes in clinical care. Further work may be needed to elucidate the reasons behind postmarketing study delays.

Though several studies and government reports investigated the time between product approval and postmarketing study completion, not all studies and government reports evaluating timeliness considered the exact same definition. For example, the time between drug approval and postmarketing study completion may differ by several months from the time between protocol approval and postmarketing study completion. This suggests that the magnitude of delays should not be over-interpreted, with more attention needed to characterize each type of delay.

Once postmarketing studies are fulfilled, the FDA encourages data sharing for clinical trials through the registration or publication of results [11]. PMRs and PMCs did so in either publications or registries about two-thirds to three-quarters of the time, with Accelerated Approval PMRs reporting results at a higher rate than other PMRs and PMCs. For cases in which PMRs and PMCs did not have published results, alternative explanations may exist besides manufacturer neglect or misconduct. The use of publication in a journal as a metric assumes that the model of journal publication is the most effective for sharing study results, overlooking PMRs/PMCs reports that were rejected for having trivial or common findings. This concern could be addressed if manufacturers considered publishing PMR/PMC results on preprint servers to ensure transparency.

Although PMRs and PMCs are intended to provide additional information about a product after its initial approval, the studies and government reports we identified found variable implementation of this principle. For example, the PREA sought to increase the available data on the safety, efficacy, and proper dosing of drugs in children. Completed studies under the PREA indeed reflected this goal, as most labeling changes associated with PREA studies involved

Table 2 Studies highlighting PMC and PMR timeliness

Study	Sample description	Key findings
Reviews of ostmarketing requirements and commitments		
Guinn 2021 [1]	126 PMRs and PMCs for 56 drugs with immunogenicity assessments in their labeling approved 2009-2018	Median time to fulfillment was 2.6 (range 0.47–8.2) years
Moneer 2021 [2]	128 PMRs and PMCs for 35 new vaccines approved 2006–2020	Median time from approval to completion of PMRs/PMCs was 50 months
Reviews of postmarketing commitments only		
Wallach *BMC* 2019 [8]	331 PMCs (33 PMCs for clinical trials; 27 PMCs subject to 506B reporting requirements) for 61 new drugs and biologics approved 2009–2012	Median time from approval to results reporting or publication was 65 months
Reviews of postmarketing requirements only		
Wallach *JGIM* 2019 [19]	119 clinical PMRs examining drug safety/efficacy for 66 drugs approved 2009–2012	For PMRs under PREA, median time from drug approval to protocol submission was 15 months, while the median time from protocol submission to study completion was 38 months, and the median time for primary outcome ascertainment was 3 months. For PMRs under FDAAA, median time from drug approval to protocol submission was 4 months, while the median time from protocol submission to study completion was 53 months, and median time for primary outcome ascertainment was 12 months. For PMRs under Accelerated Approval, median time from drug approval to protocol submission was 3 months, while median time from protocol submission to study completion was 72 months, and median time for primary outcome ascertainment was 46 months
Wallach *BMJ* 2018 [9]	437 PMRs (134 PMRs for postmarket prospective cohort studies, registries, and clinical trials) for 97 new drugs and biologics approved 2009–2012	Median time from approval to results reporting for all PMRs was 47 months. The median time from study completion to results reporting for postmarket prospective cohort studies, registries, and clinical trials was 15 months
Beaver 2018 [12]	Confirmatory studies for 64 cancer drugs spanning 93 indications granted Accelerated Approval December 11, 1992–May 31, 2017	Median time from Accelerated Approval to verification of benefit was 3.4 years (range 0.5–12.6)
Zettler 2018 [13]	34 clinical PMRs for 17 oncology drugs receiving Accelerated Approval 2011–2016	No pending or ongoing studies were behind original schedules
Naci 2017 [14]	38 PMRs required under Accelerated Approval for 22 new drugs approved 2009–2013	Median time from Accelerated Approval to study fulfillment was 1.3–5.3 years
Johnson 2011 [16]	PMRs for 35 cancer drugs spanning 47 indications under Accelerated Approval approved December 11, 1992–July 1, 2010	Median time from Accelerated Approval to regular approval was 3.9 (0.8–12.6) years
Winiecki 2016 [18]	24 pediatric registries included in the April 2014 version of the FDA Postmarketing Requirements and Commitments database	Median time to first patient enrollment for successful registries with pre-existing registries was 3.8 years before FDA approval, while the median time to first patient enrollment for successful registries not using pre-existing registries was 2.2 years after FDA approval. The median time to first patient enrollment for unsuccessful registries was 3.2 years after FDA approval

Table 3 Studies highlighting PMC and PMR results reporting

Article (year)	Sample description	Key findings
Reviews of postmarketing requirements and commitments		
Cruz 2017 [20]	288 reportable postmarket studies designated by FDA between 2009 and 2013 as "fulfilled"	64% of postmarket studies were published or posted to ClinicalTrials.gov by July 2016. 61% of studies were published. 30% of studies were posted to ClinicalTrials.gov. All studies for drugs receiving Accelerated Approval were published
Reviews of postmarketing commitments only		
Wallach *BMC* 2019 [8]	331 PMCs (33 PMCs for clinical trials; 27 PMCs subject to 506B reporting requirements) for 61 new drugs and biologics approved 2009–2012	76% of all studies either reported results or were published. 48% of all studies were published. 90% of all studies posted to ClinicalTrials.gov
Reviews of postmarketing requirements only		
Wallach *BMJ* 2018 [9]	437 PMRs (134 PMRs for postmarket prospective cohort studies, registries, and clinical trials) for 97 new drugs and biologics approved 2009–2012	72% of completed postmarket prospective cohort studies, registries, and clinical trials either reported results or were published. 57% of these completed studies were published
Naci 2017 [14]	38 PMRs required under Accelerated Approval for 22 new drugs approved 2009–2013	90% of completed studies published
Hwang 2019 [17]	222 PMRs required under PREA for 114 new drugs and new indications approved 2007–2014	76% of completed studies reported results
Winiecki 2016 [18]	24 pediatric registries included in the April 2014 version of the FDA Postmarketing Requirements and Commitments database	42% of registries reported results via a report to the FDA or publication

Table 4 Studies highlighting PMC and PMR study outcomes

Study	Sample description	Key findings
Reviews of postmarketing requirements and commitments		
Skydel 2021 [21]	1978 PMRs and PMCs for 343 new therapeutics approved 2009–2018	25% of postmarketing studies not related to the original indication
Guinn 2021 [1]	126 PMRs and PMCs for 56 products with immunogenicity assessments in their labeling approved 2009–2018	55% of fulfilled PMCs/PMRs led to labeling changes related to immunogenicity
Ogasawara 2018 [22]	4 PMRs and PMCs related to dose optimization for 4 biologics approved 2003–2016	No clear association observed between PMRs/PMCs and dose selection
Hung 2017 [23]	10 PMRs and 27 PMCs for all 5 biosimilars approved Jan 2015–Jun 2017	All PMRs for biosimilars were related to pediatric studies
Lu 2016 [24]	11 PMRs and PMCs related to dose optimization for 11 oncology indications approved 2010—first quarter of 2015	Five PMRs tested lower doses than the original label dose, and two PMRs/PMCs tested higher doses than the original label dose. Four PMRs/PMCs were for additional analyses to justify the original label dose
Kesselheim 2011 [25]	PMRs and PMCs for 15 orphan and 12 nonorphan cancer drugs approved 2004–2010	96% of drugs approved with at least one PMR or PMC
Reviews of postmarketing requirements only		
Gyawali 2019 [11]	93 confirmatory studies for 64 cancer drugs granted Accelerated Approval December 11, 1992–May 31, 2017	62% of indications confirmed benefit, while 9% of indications did not confirm benefit
Beaver 2018 [12]	Confirmatory studies for 64 cancer drugs spanning 93 indications granted Accelerated Approval December 11, 1992–May 31, 2017	5% of indications withdrawn from the market, while 55% of indications verified clinical benefit
Zettler 2018 [13]	34 clinical PMRs for 17 oncology drugs receiving Accelerated Approval 2011–2016	12% of drugs changed labeling after discovering serious safety risks during confirmatory trials. 18% of drugs failed to meet confirmatory trial endpoints, though remained on the market
Naci 2017 [14]	38 PMRs required under Accelerated Approval for 22 new drugs approved between 2009 and 2013	8% of indications without label updates did not confirm clinical benefit
Gaddipati 2012 [15]	PMRs and PMCs for 19 rare cancer drugs spanning 24 indications approved December 1987–May 2011	42% of products receiving Accelerated Approval discovered toxicity findings during postmarket studies leading to label revisions and 1 drug removed from market
Johnson 2011 [16]	PMRs for 35 cancer drugs spanning 47 indications under Accelerated Approval approved December 11, 1992–July 1, 2010	9% of drugs did not show benefit in their confirmatory trials
Bourgeois 2019 [26]	532 labeling changes attributed to PREA 1998–2018	PREA resulted in 532 labeling changes from 1998 to 2018 74% of labeling changes from 2014 to 2018 were attributed solely to PREA
Hwang 2019 [17]	222 PMRs required under PREA for 114 new drugs and new indications approved 2007–2014	30% of product labels without pediatric information at initial approval were updated with pediatric dosing information
Nagai 2018 [27]	81 confirmatory studies for all 63 oncology drugs approved under Accelerated Approval Dec 1992–Dec 2016	19% of hematologic malignancy indications for relapsed disease confirmed benefit in confirmatory trials
Winiecki 2016 [18]	24 pediatric registries included in the April 2014 version of the FDA Postmarketing Requirements and Commitments database	42% of registries were deemed successful, 17% as unsuccessful, and 42% as unevaluable. Success was defined as reaching target enrollment and fulfilling the stated registry objective by providing results in form of report to FDA or publication

the expansion of label indications from adult populations to pediatric populations. By contrast, studies related to Accelerated Approval PMRs emphasized that confirmatory trials often continued to use surrogate measures, sometimes the same ones used in the preapproval studies, which does not clarify clinical benefit. The agency reviews clinical protocols to provide feedback on postmarketing study design, yet the FDA has rarely sought to withdraw products from the market in situations when manufacturers do not meet PMRs [12]. Even short of withdrawal, in the 14 years since the FDAAA, the FDA has not imposed any civil monetary penalties for delayed PMRs [19].

Greater attention is also needed to assess the utility of the information generated. Study completion, particularly those with unfavorable results, often occurs shortly before the expiration of exclusivity or the introduction of a new competing product [43]. Data on whether and to what extent this occurs have important implications for the overall value of, and rationale for, post-approval study requirements.

As we conducted this study, we also found numerous editorials covering PMRs and PMCs. FDA authors Kashoki et al. [47, 48] commented on two papers included in our review [18, 19] to justify the categories of "pending" and "delayed" study status. They noted that a pending status does not imply delays to a study, and that even studies categorized as delayed may be justified in their delay. Meanwhile, other editorials have expressed concern about the timeliness of PMRs and PMCs. In 2014, Willyard summarized such viewpoints [3, 18, 21, 28, 31–33, 36, 37, 42, 43] on the use of post-approval studies, all of which concluded that more needed to be done to address the problems of delays, low completion rates, and information transparency [49]. In a legal and policy analysis of the FDA's use of PMRs, Herder commented on the FDA's shift toward a model of lifecycle regulation, offering that PMRs may be difficult to enforce due to the agency's limited legal powers and constrained resources [12].

This review has some limitations. PMR/PMC characteristics were not meta-analyzed due to the heterogeneity in study designs and overlapping study samples. For example, some published studies reported on all new therapeutics while others focused only on vaccines or oncology products, suggesting that studies could sometimes report on the same subsets of PMRs/PMCs even if the study samples had different definitions. For similar reasons, trends in completion rates over time or across study subtypes were difficult to assess, for example, because time to follow-up differed across the studies.

5 Conclusion

Even without a quantitative meta-analysis, several key conclusions emerge. To respond to evolving issues in drug review, Congress gave the FDA numerous authorities to require the generation of important evidence about approved drugs through PMRs and PMCs. Post-approval studies are commonly set at the time of drug approval, but greater attention is needed to encourage the timely completion of studies, improve the transparency of study findings, and ensure that the design and fulfillment of PMRs and PMCs leads to optimally useful information for prescribers and patients on the medications being evaluated. Further work is needed to assess the reasons for why postmarketing studies are often incomplete and delayed in addition to refining which types of PMRs/PMCs are most effective at providing clinically useful information to patients and prescribers.

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Declarations

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Conflict of interest Murray Ross and Krysten W. Joyce receive support from Kaiser Foundation Health Plan as salaried employees. Jonathan J. Darrow and Aaron S. Kesselheim receive grants/contracts from Commonwealth Fund, Greenwall Foundation, Health Action International's ACCISS program, National Institutes of Health, West Health, Novo Nordisk Foundation, and Massachusetts Health Policy Commission. Jonathan J. Darrow has royalties/licenses from Wolters Kluwer. Jonathan J. Darrow has received payments from National Cooperative Rx. Jonathan J. Darrow is involved with CURE Drug Repurposing Collaboratory (NIH-FDA) and the Swiss non-profit Molecule in an unpaid capacity. Murray Ross is a board chair for the Institute for Clinical and Economic Review and a board chair for the Network for Excellence in Health Innovation. Osman Moneer, Beatrice L. Brown, Jerry Avorn, Mayookha Mitra-Majumdar, and Catherine Pham have no interests to disclose.

Ethical approval Not required.

Author contributions OM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. OM, BLB, and ASK were responsible for the data acquisition and analyses. All authors contributed to interpretation of the findings. OM drafted the manuscript. All the authors contributed to critical revision of the manuscript for important intellectual content. ASK supervised the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the final version of the manuscript.

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Availability of data and materials Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Code availability Not applicable.

References

1. Food and Drug Administration (2020) Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products. Accessed 20 May 2021.
2. Darrow JJ, Avorn J, Kesselheim AS. FDA Approval and Regulation of Pharmaceuticals, 1983–2018. JAMA. 2020;323:164–76. https://doi.org/10.1001/jama.2019.20288.
3. Downing NS, Aminawung JA, Shah ND, et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. JAMA. 2014;311:368. https://doi.org/10.1001/jama.2013.282034.
4. Downing NS, Shah ND, Aminawung JA, et al. Postmarket safety events among novel therapeutics approved by the US food and drug administration between 2001 and 2010. JAMA. 2017;317:1854–63. https://doi.org/10.1001/jama.2017.5150.
5. Meyer RJ. Regulatory considerations for determining postmarketing study commitments. Clin Pharmacol Ther. 2007;82:228–30. https://doi.org/10.1038/sj.clpt.6100238.
6. Food and Drug Administration (2018) Postmarketing Requirements and Commitments: Introduction. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments. Accessed 6 May 2021.
7. Investigational New Drug Application: phase 4 studies, 21 CFR §312.85.
8. Pediatric Research Equity Act, Pub L No. 108-155, 117 Stat 1936 (2003).
9. Licensing: approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, 21 CFR §601.41.
10. Applications for FDA approval to market a new drug: approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, 21 CFR §314.510.
11. FDA Amendments Act of 2007, Pub L No. 110-85, 121 Stat 823, 931 (2007).
12. Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US food and drug administration, and institutional incumbency. Milbank Q. 2019;97:820–57. https://doi.org/10.1111/1468-0009.12413.
13. Kesselheim AS, Wang B, Franklin JM, Darrow JJ. Trends in utilization of FDA expedited drug development and approval programs, 1987–2014: cohort study. BMJ. 2015;351: h4633. https://doi.org/10.1136/bmj.h4633.
14. Hwang TJ, Darrow JJ, Kesselheim AS. The FDA's expedited programs and clinical development times for novel therapeutics, 2012–2016. JAMA. 2017;318:2137. https://doi.org/10.1001/jama.2017.14896.
15. Food and Drug Administration (2020) Postmarketing Requirements and Commitments: Legislative Background. https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-legislative-background. Accessed 6 May 2021.
16. Applications for FDA approval to market a new drug: other postmarketing reports, 21 CFR §314.81 (2019).
17. Food and Drug Administration (2020) Postmarketing Requirements and Commitments: Reports. https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports. Accessed 6 May 2021.
18. Fain K, Daubresse M, Alexander GC. The food and drug administration amendments act and postmarketing commitments. JAMA. 2013;310:202. https://doi.org/10.1001/jama.2013.7900.
19. Woloshin S, Schwartz LM, White B, Moore TJ. The fate of FDA postapproval studies. N Engl J Med. 2017;377:1114–7. https://doi.org/10.1056/NEJMp1705800.
20. Dauner DG, Dauner KN, Peterson ALH. FDA's unimproved enforcement of postmarketing requirements and commitments: implications for providers and patients. Res Social Adm Pharm. 2020;16:844–7. https://doi.org/10.1016/j.sapharm.2019.11.004.
21. Skydel JJ, Zhang AD, Dhruva SS, et al. US Food and Drug Administration utilization of postmarketing requirements and postmarketing commitments, 2009–2018. Clin Trials. 2021. https://doi.org/10.1177/17407745211005044.
22. Moore TJ, Furberg CD. Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US food and drug administration: the class of 2008. JAMA Intern Med. 2014;174:90. https://doi.org/10.1001/jamainternmed.2013.11813.
23. Cruz ML, Xu J, Kashoki M, Lurie P. 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;177:1207–10. https://doi.org/10.1001/jamainternmed.2017.1313.
24. Ogasawara K, Breder CD, Lin DH, Alexander GC. Exposure- and dose-response analyses in dose selection and labeling of FDA-approved biologics. Clin Ther. 2018;40:95-102.e2. https://doi.org/10.1016/j.clinthera.2017.11.012.
25. Lu D, Lu T, Stroh M, et al. A survey of new oncology drug approvals in the USA from 2010 to 2015: a focus on optimal dose and related postmarketing activities. Cancer Chemother Pharmacol. 2016;77:459–76. https://doi.org/10.1007/s00280-015-2931-4.
26. Hung A, Vu Q, Mostovoy L. A systematic review of U.S. biosimilar approvals: what evidence does the FDA require and how are manufacturers responding? J Manag Care Spec Pharm. 2017;23:1234–44. https://doi.org/10.18553/jmcp.2017.23.12.1234.
27. Hyogo A, Kaneko M, Narukawa M. Factors that influence FDA decisions for postmarketing requirements and commitments during review of oncology products. J Oncol Pract. 2018;14:e34–41. https://doi.org/10.1200/JOP.2017.023234.
28. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA. 2011;305:2320–6. https://doi.org/10.1001/jama.2011.769.
29. Moneer O, Lee CC, Avorn J, Kesselheim AS. Characteristics of postmarketing studies for vaccines approved by the US food and drug administration, 2006–2020. JAMA Netw Open. 2021;4:e218530. https://doi.org/10.1001/jamanetworkopen.2021.8530.
30. Guinn D, Madabushi R, Wang Y-M, et al. Elucidating the impact of immunogenicity assessment postapproval: a targeted analysis of immunogenicity postmarketing requirements and commitments. Clin Pharmacol Ther. 2021;109:697–704. https://doi.org/10.1002/cpt.2038.
31. Wallach JD, Luxkaranayagam AT, Dhruva SS, et al. Postmarketing commitments for novel drugs and biologics approved by the US Food and Drug Administration: a cross-sectional analysis. BMC Med. 2019;17:117. https://doi.org/10.1186/s12916-019-1344-3.

32. Wallach JD, Egilman AC, Dhruva SS, et al. Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross sectional analysis. BMJ. 2018;361: k2031. https://doi.org/10.1136/bmj.k2031.
33. Wallach JD, Egilman AC, Ross JS, et al. Timeliness of postmarket studies for new pharmaceuticals approved between 2009 and 2012: a cross-sectional analysis. J Gen Intern Med. 2019;34:492–5. https://doi.org/10.1007/s11606-018-4779-x.
34. Johnson JR, Ning Y-M, Farrell A, et al. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst. 2011;103:636–44. https://doi.org/10.1093/jnci/djr062.
35. Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US food and drug administration accelerated approval of malignant hematology and oncology drugs and biologics: a review. JAMA Oncol. 2018;4:849–56. https://doi.org/10.1001/jamaoncol.2017.5618.
36. Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. JAMA Intern Med. 2019;179:906. https://doi.org/10.1001/jamainternmed.2019.0462.
37. Naci H, Smalley KR, Kesselheim AS. Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US food and drug administration. JAMA. 2017;318:626–36. https://doi.org/10.1001/jama.2017.9415.
38. Zettler M, Nabhan C. Fulfillment of postmarketing requirements to the FDA for therapies granted oncology indications between 2011 and 2016. JAMA Oncol. 2018;4:993–4. https://doi.org/10.1001/jamaoncol.2018.0610.
39. Chen EY, Raghunathan V, Prasad V. An overview of cancer drugs approved by the US food and drug administration based on the surrogate end point of response rate. JAMA Intern Med. 2019;179:915–21. https://doi.org/10.1001/jamainternmed.2019.0583.
40. Gaddipati H, Liu K, Pariser A, Pazdur R. Rare cancer trial design: lessons from FDA approvals. Clin Cancer Res. 2012;18:5172–8. https://doi.org/10.1158/1078-0432.CCR-12-1135.
41. Nagai S, Ozawa K. Drug approval based on randomized phase 3 trials for relapsed malignancy: analysis of oncologic drugs granted accelerated approval, publications and clinical trial databases. Invest New Drugs. 2018;36:487–95. https://doi.org/10.1007/s10637-018-0572-2.
42. Hwang TJ, Orenstein L, Kesselheim AS, Bourgeois FT. Completion rate and reporting of mandatory pediatric postmarketing studies under the US Pediatric Research Equity Act. JAMA Pediatr. 2019;173:68–74. https://doi.org/10.1001/jamapediatrics.2018.3416.
43. Bourgeois FT, Kesselheim AS. Promoting pediatric drug research and labeling—outcomes of legislation. N Engl J Med. 2019;381:875–81. https://doi.org/10.1056/NEJMhle1901265.
44. Winiecki SK, Tejero-Taldo MI, Avant D, et al. Pediatric registries at the Food and Drug Administration: design aspects that increase their likelihood of success. Pharmacoepidemiol Drug Saf. 2016;25:602–5. https://doi.org/10.1002/pds.3939.
45. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol. 2015;79:357–69. https://doi.org/10.1111/bcp.12305.
46. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet. 2004;364:803–11. https://doi.org/10.1016/S0140-6736(04)16942-0.
47. Kashoki M, Lee C, Stein P. FDA oversight of postmarketing studies. N Engl J Med. 2017;377:1201–2. https://doi.org/10.1056/NEJMc1709185.
48. Kashoki M, Lee C, Jenkins J. Drug postmarketing studies. JAMA. 2013;310:2459. https://doi.org/10.1001/jama.2013.278901.
49. Willyard C. FDA's post-approval studies continue to suffer delays and setbacks. Nat Med. 2014;20:1224–5. https://doi.org/10.1038/nm1114-1224.

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