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FDA IS ISSUING MORE POSTMARKETING REQUIREMENTS, BUT CHALLENGES WITH OVERSIGHT PERSIST

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EXECUTIVE SUMMARY: FDA is Issuing More Postmarketing Requirements, but Challenges with Oversight Persist
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WHY WE DID THIS STUDY

FDA approves new drugs for sale in the United States through the new drug application (NDA) review process. FDA requires all new drugs to undergo clinical testing to demonstrate their safety and efficacy prior to approval. However, premarket clinical trials may not always identify or fully characterize risks. Postmarketing research can provide additional information about the risks, benefits, and optimal use of an approved drug. In 2006, the Office of Inspector General (OIG) found that FDA could not readily identify whether or how timely postmarketing studies were progressing toward completion, and that FDA lacked an effective monitoring system for postmarketing studies. Since then, the Food and Drug Administration Amendments Act (FDAAA) expanded FDA's authority to require postmarketing studies and to take enforcement action when sponsors are out of compliance. This study follows up on OIG's previous work in light of FDA's expanded authority.

HOW WE DID THIS STUDY

We analyzed data from FDA's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) for all prescription drug PMRs initiated in FY 2008 through 2014. We reviewed all FY 2014 Annual Status Reports (ASRs) and FDA ASR review documents for PMRs initiated in our review period. We also reviewed all noncompliance communication from FDA to sponsors of PMRs from FY 2008-FY 2014. Finally, we interviewed FDA staff.

WHAT WE FOUND

FDA used its FDAAA authority to issue half of all PMRs in FY 2008 through FY 2014, and required multiple types of studies and clinical trials to fulfill PMRs. It issued PMRs for both supplemental applications and NDAs, and the majority of PMRs were related to NDAs. FDA issued PMRs more often for NDAs reviewed through expedited programs than for non-expedited NDAs. Sponsors are completing most PMRs according to schedule, but a few PMRs are delayed. For about half of all PMRs fulfilled in FY 2014, FDA required sponsors to make labeling changes and/or take other actions to ensure the safety of their drugs. However, FDA continues to have problems with its data management system and work processes, which hinder its ability to track PMRs.

WHAT WE RECOMMEND

FDA should:
(1) Provide a standardized form for ASRs, ensure that they are complete, and require sponsors to submit them electronically. Standardized forms and electronic submission

would provide FDA staff with comparable information across ASRs and eliminate the need for manual data entry, enhancing FDA's ability to track PMRs.
(2) Build capacity in DARRTS to support PMR oversight. Automated reports could improve FDA staff's ability to identify pending ASR due dates, PMR statuses that are overdue for updates, or missing and late ASRs.
(3) Determine the reasons why some PMRs have been delayed for years, and take action as appropriate.

FDA implemented our recommendation to determine the reasons some PMRs have been delayed and concurred with our other two recommendations.

TABLE OF CONTENTS

Objectives 1

Background 1

Methodology 6

Findings.....8

FDA used its FDAAA authority to issue half of all PMRs from FY 2008 through FY 2014 8

FDA issued more PMRs NDAs than for supplemental applications 9

Although a few PMRs are delayed, sponsors are making progress toward completing most PMRs according to schedule.....11

For half of all PMRs fulfilled in FY 2014, FDA required sponsors to take action, most often related to safety 14

FDA monitors PMRs, but shortcomings in FDA's data management system limit its ability to track PMR progress 14

Conclusion and Recommendations.....19

Agency Comments and Office of Inspector General Response.....21

Appendix.....22

Acknowledgments.....26

OBJECTIVES

To determine:

1. The extent and nature of postmarketing studies in the context of the Food and Drug Administration (FDA) postmarketing requirements (PMR) for certain drugs;
2. The extent to which sponsors complete PMRs;
3. How and the extent to which FDA oversees PMRs; and
4. How and the extent to which FDA takes action based on PMRs.

BACKGROUND

FDA approves new drugs for sale in the United States through the new drug application review process. FDA requires that all new drugs undergo clinical testing to demonstrate their safety and efficacy prior to approval. However, premarket clinical trials may not always identify or fully characterize all risks related to the use of a drug. Postmarketing research can provide additional information about the risks, benefits, and optimal use of an approved drug.

Previous work by the Office of Inspector General (OIG) identified problems in FDA's monitoring of PMRs. In 2006 OIG recommended, among other things, that FDA improve its information management system for monitoring postmarketing studies and ensure that postmarketing studies are monitored and annual status reports (ASRs) are validated. FDA agreed to these recommendations and has implemented them.[1] In 2009, the Government Accountability Office (GAO) similarly found that FDA has not routinely met its goal of reviewing status reports within 90 days to verify information and the status of postmarketing studies.[2] More recently, in 2015 GAO found that problems with FDA's postmarket study data restrict FDA's ability to perform systematic oversight of postmarket drug safety.[3]

[1] Office of Inspector General, FDA's Monitoring of Postmarketing Study Commitments, June 2006. Accessed online: http://oig.hhs.gov/oei/reports/oei-01-04-00390.pdf on 16 October 2015.

[2] Government Accountability Office, FDA Needs to Enhance its Oversight of Drugs Approved on the Basis Use of Surrogate Endpoints, September 2009. Accessed online: http://www.gao.gov/assets/300/295762.pdf on 16 October 2015.

[3] Government Accountability Office, Drug Safety: FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement, December 2015. Accessed online: http://www.gao.gov/assets/680/674183.pdf on 3 March 2016.

Since OIG last evaluated FDA's oversight of postmarketing research, the Food and Drug Administration Amendments Act (FDAAA) expanded FDA's authority to require postmarketing studies and to take enforcement action against sponsors who fail to comply with the requirements of section 505(o)(3) of the Food, Drug and Cosmetic Act (FD&C Act). FDA's expanded authority to require postmarketing studies is an important tool for assessing serious risk related to the use of a drug.

Postmarketing Requirements

Postmarketing studies and clinical trials could measure an approved drug's clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology.[4] FDA may use information from these studies to request an update to a drug's label, approve a drug for new uses, require additional risk management interventions, or, in rare cases, seek to have the manufacturer withdraw a drug from the market. Likewise, FDA may determine that the PMR results indicate that no further action is needed.

In 2007, Section 901 of the FDAAA amended and added section 505(o) of the FD&C Act. Section 505(o) of the FD&C Act authorizes FDA to require postmarket studies or clinical trials involving an approved drug or biological product to assess known or potential serious risks related to its use.[5] Postmarketing studies and clinical trials required by FDA under this or other statutory authority are called PMRs.[6,7]

Prior to 2007, FDA could only require that applicants conduct postmarketing research under the following circumstances:

- Pediatric Research Equity Act (PREA) PMRs: FDA may approve a drug that is ready for approval for use in adults but has not been studied in a relevant pediatric population. In these cases, FDA may defer pediatric studies under PREA.
- Accelerated Approval PMRs: Under the Accelerated Approval Pathway, FDA may approve a drug based on a surrogate or intermediate clinical endpoint. These approvals require

[4] 21 CFR 314.81(b)(2)(vii).

[5] Section 901 of the FDAAA (P.L. 110-85, Sept. 27, 2007) added § 505(o)(3) to the FFDCA (21 U.S.C. § 355(o)(3)).

[6] FDA, Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. Accessed online: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf on 2 March 2016.

[7] All other postmarketing studies are called postmarketing commitments. Postmarketing commitments differ from PMRs because the studies are proposed by FDA, not required. An applicant may agree to conduct the studies, and so enters into a commitment with FDA. Our evaluation focused on PMRs.

postmarketing studies or clinical trials to verify the clinical benefit.[8]

- Animal Efficacy Rule PMRs: When human clinical trials cannot be conducted ethically, FDA may approve a drug based solely on animal studies. In these cases, FDA may require the sponsor to conduct postmarketing studies in humans, when feasible and ethical.[9]

In addition to the authorities listed above, under FDAAA, FDA can require one or more PMRs at the time of a drug's approval or after approval for one or more of the following reasons:

- to assess a known serious risk related to the use of the drug,
- to assess signs of serious risk related to the use of the drug, and/or
- to identify an unexpected serious risk when available data indicate the potential for a serious risk.[10]

FDA may issue PMRs related to NDAs or supplemental applications. A sponsor may submit a supplemental application to amend an existing approved application. There are four types of supplemental applications:

- Efficacy Supplement: application proposing one or more changes to the product labeling, e.g., to add or modify an indication or claim, revise the dose, or to significantly alter the intended patient population, among other changes.[11]
- Labeling Supplement: application proposing labeling changes other than those defined by efficacy, manufacturing, and Risk Evaluation and Mitigation Strategy (REMS) supplements.[12]
- Manufacturing Supplement: application for chemistry, manufacturing, and control changes.[13]
- REMS Supplement: application proposing a new post-approval REMS or a modification of an approved REMS.[14]

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[8] Section 506(b)(2)(A) of the FD& C Act; 21 CFR 314.510.

[9] 21 CFR § 314.610(b)(1).

[10] FDA, Guidance for Industry Postmarketing Studies and Clinical Trials-Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, April 2011. Accessed online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf on 16 October 2015.

[11] 21 CFR § 314.3(b).

[12] 21 CFR § 314.70.

[13] 21 CFR § 314.70.

[14] Section 505-1(g) and (h) of the FD&C Act.

Expedited Programs

Postmarketing research may be particularly useful for applications reviewed through expedited programs. FDA has four expedited programs, which are designed to facilitate and expedite development and review of new drugs to address an unmet medical need in the treatment of a serious condition.[15] The four programs are:

- Accelerated Approval Pathway,
- Priority Review Designation,
- Fast Track Designation, and
- Breakthrough Therapy Designation.

FDA Procedures for Issuing PMRs

To issue a PMR, either at the time of approval or after approval, FDA notifies the sponsor by letter explaining the purpose and details of the required research. When FDA notifies a sponsor of a PMR, it also requests a proposed timetable for completion. Both FDA and the sponsor review and agree on the final timetable for completing each PMR.

FDA Oversight of PMRs

Annual Status Reports. A sponsor must annually report to FDA on the status of each open PMR.[16] In general, FDA requires annual reports (hereinafter referred to as annual status reports, or ASRs), but it may require additional reporting on a case-by-case basis.[17] FDA and the sponsor agree to report due dates as part of the timetable for completing a PMR.

Among other things, these reports must include the status of the PMR. Based on a review of the ASR and information submitted by the sponsor, FDA assigns each PMR to one of 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.

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[15] FDA, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. Accessed at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf on 06 January 2015.

[16] Sections 21 CFR 314.81(b)(2)(vii), 505(o)(3)(E)(ii), and section 506B of the FD&C Act.

[17] Applicants must submit status reports within 60 days after the anniversary date of the application's approval. FDA, Postmarketing Requirements and Commitments: Frequently Asked Questions. Accessed at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm#q8 on 16 October 2015.

- 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.
- 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.
- 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.
- Released: FDA informed the sponsor in writing that it is released from its obligation to conduct the study or clinical trial.[18]

Administrative and Enforcement Actions. FDAAA authorizes FDA to take actions against sponsors who fail to meet the obligations of a PMR issued under section 505(o)(3) of the FD&C Act (hereinafter referred to as FDAAA PMRs). In determining whether to take enforcement action, FDA assesses whether a sponsor is out of compliance with the terms of a PMR without good cause. FDA has the discretion to determine good cause. If a sponsor fails to comply with FDAAA PMR requirements without good cause, FDA may bring misbranding charges or impose civil monetary penalties, among other actions. FDA typically advises sponsors of instances of noncompliance by issuing an untitled letter or warning letter prior to pursuing enforcement actions, which allows sponsors an opportunity to voluntarily come into compliance. However, FDA is not obligated to provide prior notice through an untitled or warning letter before taking an enforcement action.

FDA may also take action against sponsors who fail to complete a PMR under Accelerated Approval, the Animal Efficacy Rule, or PREA. For a drug approved under Accelerated Approval or the Animal Efficacy Rule, FDA has the authority to withdraw its approval after appropriate notice

[18] FDA, Manual for Policies and Procedures, MAPP 6010.2: Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments. Accessed online:
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM174552.pdf on 2 March 2016.

and an opportunity for a hearing if the sponsor fails to conduct a PMR with due diligence. Although FDA may not withdraw the approval of a drug if a sponsor fails to submit a pediatric assessment under PREA, this failure could result in the drug being considered misbranded and the FDA could then initiate an enforcement action.

Related Work

As previously noted, in 2006 OIG issued a report titled *FDA's Monitoring of Postmarketing Study Commitments*. In 2009, GAO released a report titled *FDA Needs to Enhance its Oversight of Drugs Approved on the Basis Use of Surrogate Endpoints,* which similarly looked at FDA's oversight of postmarketing studies. In 2015, GAO released a report titled *Drug Safety: FDA Expedites Many Applications, but Data for Postapproval Oversight Need Improvement,* which included findings on FDA's postmarket study data.

METHODOLOGY

Scope

This study focuses on FDA's PMRs related to NDAs and supplemental applications (hereinafter referred to together as applications) for drugs approved between FY 2008 and 2014. This time period coincides with FDA's authority to initiate PMRs under FDAAA.

Our review includes all drug PMRs that FDA issued from FY 2008 through 2014. We excluded postmarketing commitments because they are voluntary agreements, not requirements. For workload management purposes, we excluded PMRs for biologic license applications and also limited a subset of our analysis to PMRs for FY 2014. We looked at all FY 2014 ASR and FDA ASR review documents for PMRs issued in our review period. We also focused our analysis of fulfilled PMRs on those completed in FY 2014.

Data Collection and Analysis

We used data from six sources:

- FDA's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS). FDA uses DARRTS to record PMRs and track their status. DARRTS also contains ASRs.
- Non-compliance letters including untitled letters and warning letters as well as other FDA communications of non-compliance.
- Fulfilled letters, which are letters that FDA sent to sponsors in FY 2014 as notification that a PMR is fulfilled.

- Structured interviews with staff in FDA's Center for Drug Evaluation and Research.
- Documents related to FDA review of ASRs.
- Documents related to actions taken by FDA in response to PMRs.

Standards

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

FDA used its FDAAA authority to issue half of all PMRs from FY 2008 through FY 2014

In this 7-year period, FDA issued 1,256 PMRs for 468 applications. FDA used its FDAAA authority to issue about half (52 percent, or 657) of all PMRs in this time period (see table 1). Prior to FDAAA, FDA could not have required these PMRs. FDAAA authorized FDA to issue PMRs to assess a known serious risk related to the use of a drug; to assess a signal of a serious risk related to the use of a drug; or to identify an unexpected serious risk when available data indicates the potential for a serious risk. FDA may issue FDAAA PMRs at the time of approval, or after approval if FDA becomes aware of new safety information.

Table 1: Authorities Under Which FDA Issued PMRs From FY 2008–FY 2014

Authority Used to Issue PMR	PMRs Issued in FY 2008 – FY 2014 *n (Percent of All PMRs)*
FDAAA, n (%)	657 (52%)
Other PMR Authorities, n (%)	599 (48%)
PREA	*544*
Accelerated Approval	*54*
Animal Efficacy Rule	*1*
Total	*1,256*

Source: OIG analysis of FDA DARRTS data, FY 2008–FY 2014.

The number of PMRs that FDA issued increased by 111 percent from FY 2008 to FY 2009, and then remained fairly consistent through FY 2014 (see table 2).

Table 2: Total PMRs by Establishment Fiscal Year

PMR Establishment Fiscal Year	All PMRs
FY 2008	89
FY 2009	188
FY 2010	168
FY 2011	194
FY 2012	188
FY 2013	222
FY 2014	207
Total	*1256*

Source: OIG analysis of FDA DARRTS data, FY 2008–FY 2014.
*FDA closed and then, at later dates, re-established five of these PMRs. OIG used the original PMR establishment dates for our analysis.

FDA issued the remainder (48 percent, or 599) of PMRs during this time under the authorities that existed prior to its FDAAA authority. FDA issued most of these PMRs (43 percent, or 544) under its PREA authority. PREA authorizes FDA to issue PMRs for certain drugs that are not

adequately labeled for use in pediatric populations. FDA also issued some PMRs (4 percent, or 54) under its Accelerated Approval authority and 1 under its Animal Efficacy Rule authority (see table 2).

FDA required sponsors to complete various types of postmarketing studies and clinical trials to fulfill PMRs. The research questions that a PMR is intended to answer also determine the type of study or clinical trial the sponsor conducts. For example, some questions can be answered with studies completed in a laboratory, while other questions require a clinical trial. FDA required many different types of studies: 28 percent (343) of the studies in our time period were clinical trials; the remainder of the studies conducted during our review time period, 72 percent (876), were studies that were not clinical trials, such as observational studies, clinical pharmacology studies, and registries of people taking the drug.[19]

FDA issued more PMRs for NDAs than for Supplemental Applications

Applications with PMRs represent about 2.5 percent of the 19,029 applications FDA approved in this 7-year period. The majority of the applications that FDA approved during this time period were supplemental applications (97 percent) and the remainder were NDAs (see tables 3 and 4). Of the 468 applications with PMRs, just over two-thirds (324) were NDAs. The rest were supplemental applications (144). FDA issued more PMRs related to efficacy supplemental applications than any other type of supplemental application (see table 3).

Table 3: Total Approved Supplemental Applications and Supplemental Applications With PMRs by Approval Fiscal Year

Application Approval Fiscal Year	All Approved Supplemental Applications	All Supplemental Applications with PMRs	Efficacy Supplemental Applications With PMRs	Labeling, Manufacturing, and REMS Supplemental Applications With PMRs
FY 2008	2450	20	13	7
FY 2009	2536	24	16	8
FY 2010	2472	25	17	8
FY 2011	2800	21	18	3
FY 2012	2869	16	11	5
FY 2013	2659	13	12	1
FY 2014	2660	25	14	11
Total	*18446*	*144*	*101*	*43*

Source: OIG analysis of FDA DARRTS Data, FY 2008–2014.

[19] We could not determine the study type for 37 PMRs from FDA DARRTS Data. According to FDA, these data were not captured in DARRTS partly because data entry staff was unable to easily determine the study type based on the study description in the letter establishing the PMR.

Table 4: Total Approved NDAs and NDAs With PMRs by Approval Fiscal Year

Application Approval Fiscal Year	Total Approved NDAs	NDAs with PMRs
FY 2008	74	35
FY 2009	93	57
FY 2010	72	41
FY 2011	82	47
FY 2012	79	41
FY 2013	89	51
FY 2014	94	52
Total	*583*	*324*

Source: OIG analysis of FDA DARRTS Data, FY 2008–2014

Furthermore, FDA issued PMRs more often for expedited NDAs than for non-expedited NDAs. Of the 115 expedited NDAs, 73, or 63 percent, had PMRs (see table 5).[20] This compares to 51 percent of non-expedited NDAs with PMRs.

FDA may issue more than one PMR for an application; more than half of all applications with a PMR had multiple PMRs. The number of PMRs issued per application ranged from 1 to 14.

Table 5: Expedited NDAs and Associated PMRs for FY 2008–FY 2014

Approval Fiscal Year	All Approved NDAs	All Approved Expedited (Excluding Accelerated Approval) NDAs	Expedited (Excluding Accelerated Approval) NDAs with PMRs
FY 2008	74	12	3
FY 2009	93	19	13
FY 2010	72	11	8
FY 2011	82	19	16
FY 2012	79	17	9
FY 2013	89	16	10
FY 2014	94	21	14
Total	*583*	*115*	*73*

Source: OIG Evaluation of FDA DARRTS data, FY 2008–FY 2014.

[20] For this analysis, "expedited NDAs" includes those approved drugs that were reviewed through breakthrough therapy, fast track, or priority review designation. We excluded applications that were reviewed through the accelerated approval program from this analysis because PMRs are always required for approved applications reviewed through this pathway. However, applications may be reviewed through multiple expedited programs simultaneously. Therefore, by excluding accelerated approval applications, we have also excluded some applications that were reviewed under other expedited programs.

Although a few PMRs are delayed, sponsors are making progress toward completing most PMRs according to schedule

FDA determined that the FY 2014 status of most PMRs established from FY 2008 through FY 2014 was either pending, ongoing, or fulfilled (see table 6). When FDA issues a PMR, FDA and the sponsor agree to a timetable for completion that includes dates by which the sponsor agrees to complete study milestones, such as submitting the final study protocol. PMRs are likely to be pending, or not expected to have started yet, in the year they are issued. PMR status categories progress from pending to ongoing, submitted, and fulfilled. FDA considers a PMR fulfilled once it has reviewed the completed study and notified the sponsor in writing that the study meets FDA requirements.

A PMR could also be delayed, terminated, or released at any point. PMRs may be terminated or released for many reasons. For example, a sponsor may terminate a PMR if it decides to remove the drug from the market. FDA may release a PMR if it determines the study is not feasible, if the PMR is superseded by another study, if FDA determines the PMR is not needed, or if the sponsor withdraws its application to market the drug.

Table 6: FY 2014 Status of PMRs Established FY 2008-FY 2014

PMR Status Category	PMRs n (Percent)
Pending	422 (34%)
Ongoing	260 (21%)
Submitted	48 (4%)
Fulfilled	291 (23%)
Delayed	90 (7%)
Terminated	5 (0.4%)
Released	140 (11%)
Not Feasible	55
Superseded	49
Not Needed	27
Not Marketed	9
Total	*1,256*

Source: OIG analysis of FDA DARRTS data, FY 2008–FY 2014.
Note: Percentages do not total 100 due to rounding.

Seven percent (90) of PMRs were delayed in FY 2014.

Of those PMRs that FDA categorized as delayed in FY 2014, 32 were delayed for 1 year, 34 for 2 years, and 24 for 3 to 5 years (see table 7). Of the 89 PMRs established in FY 2008, 7 were classified as delayed in FY 2014, 6 years after FDA issued the PMR.

Table 7: PMRs Delayed in FY 2014

Years Delayed	Number of PMRs Delayed in FY 2014 n (Percent)
1	32 (36%)
2	34 (38%)
3	16 (18%)
4	4 (4%)
5	4 (4%)
Total	*90*

Source: OIG analysis of FDA DARRTS data, FY 2008-FY 2014.

According to FDA, sponsors may have good reasons for these delays. For example, a PMR may fall behind schedule because the sponsor and FDA have not reached an agreement on the study design or because patient enrollment in a clinical trial is taking longer than planned. For example, in one ASR for a PMR involving a clinical trial, the sponsor wrote, "Clearly, the enrollment is challenging and is behind schedule."

When a PMR is behind schedule, FDA typically communicates with the sponsor to determine the extent and reason for the delay. In some circumstances, FDA may work with the sponsor to establish a revised timetable for completion.[21] In fact, 30 PMRs that were delayed in FY 2014 had revised timetables.

For FDAAA PMRs, FDA determines whether there is a good cause for delay. If the sponsor demonstrates good cause, FDA does not consider the sponsor to be out of compliance. FDA found good cause for delay and issued good cause letters for 5 of the 45 FDAAA PMRs that were delayed in FY 2014, which indicates that FDA assessed the sponsor's explanation for the delay, and that FDA determined the sponsor had good cause.[22]

FDA ultimately may decide to take action, such as issuing an untitled letter or a warning letter, against a sponsor of a delayed FDAAA PMR who fails to demonstrate good cause.

One-third of PMRs established from FY 2008 through FY 2014 were pending in FY 2014.

Of the PMRs with pending status in FY 2014, most were established in FY 2013 or FY 2014 (see Figure 1). Among the PMRs with pending status in FY 2014 were 7 established in FY 2008. Pending status indicates that the PMR study has not started, but that the sponsor has not yet missed the milestone due date for submitting the final study protocol. PMRs are

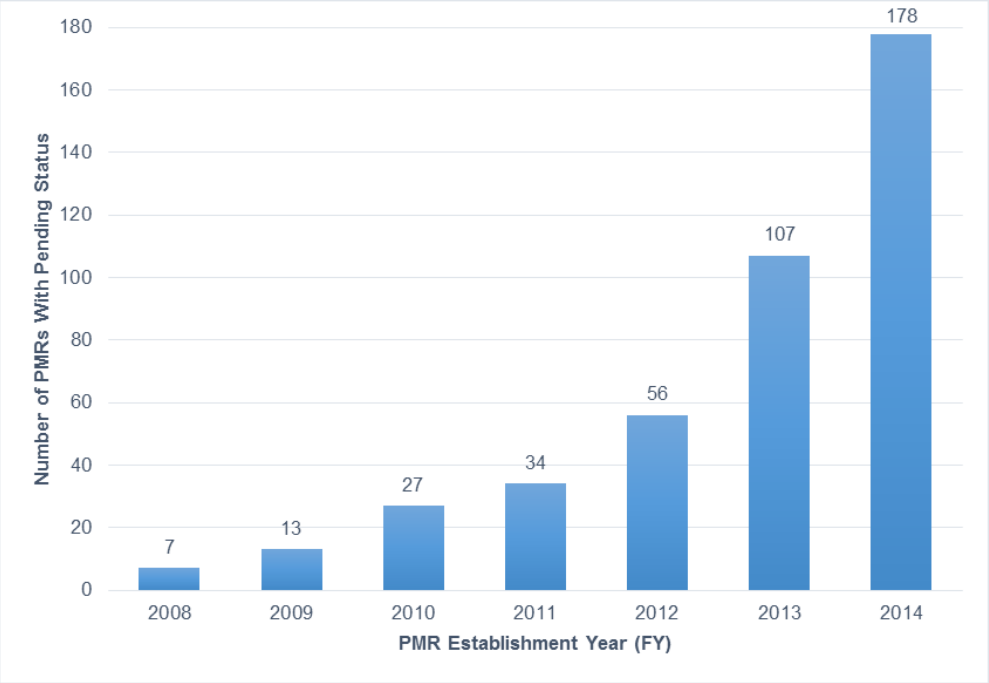
[21] FDA determines the status of a PMR based on the original timetable for completion. However, for PREA PMRs, FDA determines the status based on the revised timetable.

[22] We limited our review of good cause letters to those FDA issued in FY 2014. FDA may have made a good cause determination for these PMRs in years prior to FY 2014.

often pending after FDA issues them, for example to allow time for the sponsor to design the study and for FDA to review that design.

PMRs vary in the amount of time it takes for the study to begin (i.e., the duration that the PMR is pending). In our time period, the number of years a PMR had pending status ranged from 0 to 7 years, with a median of 1 year in pending status. The variability reflects, among other factors, the type of PMR required (e.g., clinical trial or observational study) and the anticipated time it will take for the trial or study to start. FDA staff told us that the time it takes for a sponsor to notify it that the trial or study began and for FDA staff to update the status may inflate the amount of time a PMR is pending.

Figure 1: Number of Pending PMRs by Fiscal Year in Which They Were Established



Source: OIG analysis of FDA DARRTS data, FY 2008–FY 2014.

For half of all PMRs fulfilled in FY 2014, FDA required sponsors to take action, most often related to safety

FDA may request the sponsor to take action, such as adding safety information to a drug's label, based on what it learns from a PMR, or FDA may decide that the results of a PMR prove that a signal of risk does not indicate a real threat and decide that no further action is needed. FDA required sponsors to take action 61 times in light of information from 58 of the 108 PMRs fulfilled in 2014 (see table 8).

Table 8: Actions Requested by FDA Based on the Results of PMRs Fulfilled in FY 2014.

FDA Requested Action	Number
Requested the sponsor make changes to the drug's label regarding safety information	32
Requested the sponsor make changes to the drug's label regarding the drug's efficacy	27
Issued a new PMR	1
Modified the Sponsor's REMS* for the Drug	1
Total	61

Source: OIG analysis of FDA data, FY 2014.

*FDA may require a REMS to manage a serious risk associated with a drug

FDA monitors PMRs, but shortcomings in FDA's data management system limit its ability to track PMR progress

FDA received 239 FY 2014 ASRs and reviewed 87 percent (209) of them.[23] FDA's standard is to review ASRs within 90 days of receipt.[24] FDA met that standard for 81 percent (170) of the FY 2014 ASRs it reviewed. DARRTS is the data management system FDA uses to track PMRs and the corresponding ASRs, and to identify sponsors that are out of compliance with the terms of a PMR, such as the timetable for completion. FDA told us that DARRTS does not automatically generate reports of late ASRs, or PMRs with upcoming ASR due dates. FDA staff may independently generate this information, but DARRTS is not designed in a way that allows staff to readily identify late or upcoming ASRs. This can hinder FDA's ability to track PMR progress.

[23] These ASRs covered approximately 790 PMRs. We cannot determine the exact number because 19 percent of these ASRs lacked PMR identification numbers.

[24] FDA, Guidance for Industry: Reports on the Status of Postmarketing Study Commitments – Implementation of 130 of the Food and Drug Administration Modernization Act of 1997. Accessed online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080569.pdf on 2 March 2016.

FDA sent 32 noncompliance letters to sponsors of PMRs in FY 2014.

These letters correspond to nine of the PMRs that were delayed in FY 2014 (see table 9). Not all delayed PMRs resulted in noncompliance action. A sponsor of a delayed PMR may nonetheless be in compliance if, for example, the PMR is an FDAAA PMR, and the sponsor has demonstrated good cause for delay.[25] FDA also may work with sponsors to achieve compliance without taking official action. For example, sponsors of delayed PMRs established under non-FDAAA authority may provide an explanation sufficient to justify not adhering to the original schedule.

Before FDA can take noncompliance action, it must determine that a sponsor of an FDAAA PMR is without good cause, which FDA has the discretion to define.[26] Good cause applies to FDAAA PMRs, not PMRs issued under any other authority (i.e., PREA, Accelerated Approval, or the Animal Efficacy Rule).

Table 9: PMR Noncompliance Actions FDA Took for PMRs Established From FY 2008-FY 2014

Action	Number of Letters
Notification of noncompliance with PREA letter	22
Notification of missed PMR milestone letter	4
Failure to demonstrate good cause memo	3
Failure to respond to notification of missed PMR milestone letter	1
Untitled letter	1
Warning letter	1
Total	*32*

Source: OIG analysis of FDA data, FY 2014.

Of the 32 noncompliance actions FDA took during this time period, 22 related to PREA PMRs for which the sponsor either failed to meet milestone dates for submitting required information, failed to request a deferral extension, or failed to fulfill a PMR. Of the remaining noncompliance actions, eight were related to FDAAA PMRs for which the sponsor either failed to meet milestone dates, failed to show good cause, or failed to respond to FDA correspondence.

[25] For the purposes of this report, "noncompliance action" refers to the following letters and memos: notification of noncompliance with PREA letter, notification of missed PMR milestone letter, failure to demonstrate good cause memo, failure to respond to notification of missed PMR milestone letter, untitled letter, and warning letter.

[26] As of March 2016 FDA had not released guidance to industry or FDA staff on its definition of good cause.

FDA also issued one warning letter related to PMRs established from FY 2008 through FY 2014. Prior to issuing that warning letter, FDA sent seven written correspondences to the sponsor from May 2010 to February 2012 in an attempt to resolve questions about a PMR. The correspondence FDA sent include, in the order FDA sent them:

- two general advice letters requesting clarification and additional information,
- three informal emails following up on FDA's requests,
- one formal failure to respond letter, and
- one failure to demonstrate good cause memo.

FDA issued the warning letter in February 2012, after it determined that the sponsor was out of compliance and failed to show good cause. In the warning letter, FDA informed the sponsor that the product was misbranded due to the sponsor's violation of section 505(o) of the FD&C Act. The final correspondence from FDA is a close-out letter sent 1 year after the warning letter and 11 months after the sponsor's response to the warning letter. The close-out letter states that FDA determined that the sponsor addressed all the violations in the warning letter.

FDA could not readily locate all FY 2014 ASRs due to challenges with ASR format, data management systems, and its ASR review process.

Since our 2006 report in which we identified problems with FDA's management system for postmarketing studies and recommended improvements, FDA began using DARRTS to track PMRs. However, that system does not fully resolve the challenges FDA faces in tracking PMRs. For example, despite OIG's multiple requests and four separate ASR data submissions from FDA, OIG cannot independently verify that we received ASRs for all open PMRs in FY 2014 because of missing data.[27]

The lack of a standard format for ASRs makes it difficult for FDA to track PMRs and ASRs and to extract data from ASRs. For example, some ASRs are many pages long and include detailed information, while others are just a few sentences.

In addition to variation in format, ASRs sometimes lacked required information. For example, sponsors did not include PMR identification numbers in about 19 percent (46) of the 239 ASRs that covered at least

[27] Open PMRs are those with any status other than released or fulfilled.

790 PMRs, and 12 ASRs did not include PMR status.[28] FDA relies on this basic information to track the progress of PMRs. OIG issued a similar finding in 2006 when a review of ASRs revealed that they lacked required elements and information that would be useful in monitoring the progress of postmarketing studies.

Additionally, DARRTS does not automatically produce aggregate reports of ASR due dates and submitted ASRs. According to FDA, DARRTS does not track PMRs on the individual PMR-level and does not consistently link ASRs to individual PMRs. Rather, sponsors submit ASRs to their application files, and ASRs are tracked by NDA number. Although DARRTS does not produce an automated report of ASR due dates, FDA staff can take steps to generate that information independently. DARRTS also lacks the capability to alert staff when ASRs either are approaching a due date or overdue. These limitations lead FDA tracking coordinators to develop their own manual systems for monitoring ASRs.

The processes for reviewing and recording ASRs present another challenge. Currently sponsors submit ASRs in a format that requires FDA to extract and record data manually, rather than uploading the ASR data directly to DARRTS. Sponsors submit ASRs to their application file, and then FDA review and project management staff are notified by an automated email. Once review staff have completed their review, FDA's data-entry staff are notified by an automated email. Data entry staff then extract the PMR status and other information and record it in DARRTS. FDA told us that this process can cause delays in the timely updating of PMR status.

According to FDA, its current ASR review process may also lead to delays in status updates and inaccuracies in PMR status data. For example, we identified PMRs with an FY 2014 status of pending, ongoing, delayed, or submitted that did not have an updated status in DARRTS for FY 2014. We identified 53 out of 825 open PMRs for which FDA last updated the status in FY 2012, 7 for which the last update was in FY 2011, and 3 that were last updated in FY 2010. The lack of a status update could indicate that FDA did not receive a status update from the sponsor for FY 2014 or that FDA received an update but failed to enter the status in its system. This raises questions about the accuracy of the PMR status data in DARRTS and makes it difficult to track PMR status data by year.

FDA reported that it is taking steps to improve its system for tracking ASRs, including developing automated DARRTS reports of upcoming

[28] Because many ASRs lacked PMR identification number, we could not determine the exact number of PMRs associated with FY 2014 ASRs. Analysis of ASRs that did not include PMR status was based on FDA's ASR review sheets, of which 31 are missing.

ASR due dates and overdue ASRs, and providing additional training for data entry and report review staff. FDA also is considering its options for improving status report submissions, including whether FDA has the authority to require sponsors to submit ASRs electronically.

CONCLUSION AND RECOMMENDATIONS

PMRs are important in helping FDA further evaluate new drugs. For PMRs to be effective, FDA must be able to fully account for them. However, FDA's system for overseeing PMRs is not yet up to the task.

In 2006, the OIG found problems with FDA's oversight of postmarketing studies and made recommendations for improvement. FDA concurred with OIG's recommendations to improve its data management system for monitoring postmarketing studies and validating ASRs. In 2007, FDAAA expanded FDA's authority to require PMRs to assess or identify serious risks related to the use of a drug. FDA has taken advantage of its expanded authority. FDA used its FDAAA authority to issue half of all PMRs in FY 2008 through FY 2014 and issued at least one PMR for 43 percent of expedited applications. FDA also required sponsors to take additional actions to improve the safe use of about half of all drugs approved in FY 2014 that were required to complete a PMR. However, continued problems with the data management system and work processes have hindered FDA's ability to track PMRs.

Therefore, we recommend that FDA should:

Provide a standardized form for ASRs, ensure that they are complete, and require sponsors to submit them electronically

Although FDA requires sponsors to include certain information in ASRs, format variability and missing information can hinder FDA's ability to track ASRs. By creating a standard form for ASRs and requiring sponsors to submit them electronically in a format that eliminates the need for manual data entry, FDA staff could have comparable information on each ASR and upload ASR data to DARRTS. FDA should ensure that ASRs are complete upon submission, and notify sponsors when ASRs are incomplete. These steps should enhance FDA's ability to track PMRs.

Build capacity in DARRTS to support PMR oversight

Automated reports from DARRTS on the status of ASRs could improve FDA staff's ability to identify pending ASR due dates, PMR statuses that are overdue for updates, or missing and late ASRs. To improve the utility of DARRTS for overseeing PMRs, FDA could:

- Add reports to DARRTS for tracking ASRs and PMR statuses,
- Automate work processes to alert data entry staff that an ASR has been reviewed and should be entered into DARRTS, and

- Conduct routine quality assurance of DARRTS data to ensure completeness.

Determine the reasons that some PMRs have been delayed for years, and take action as appropriate

We found four PMRs that have been delayed for 4 years, and four that have been delayed for 5 years. FDA should review these PMRs and its data to determine if they truly are delayed, or only appear to be delayed because FDA has not updated their status in DARRTS. FDA should take actions appropriate to resolve these delayed PMRs.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA concurred with two of our recommendations and implemented the third.

FDA concurred with our recommendation regarding a standardized form for ASRs, ensuring their completeness, and requiring electronic submission. It stated that it is exploring its options for standardizing the ASR form and for requiring sponsors to submit them electronically. FDA also stated that it is revising its policies and procedures to ensure that staff are consistently checking that ASRs are complete and following up with sponsors to obtain missing information.

FDA also concurred with our second recommendation to build capacity in DARRTS to support PMR oversight. It has initiated efforts to make standard PMR reports available to staff to facilitate the timely updating of PMR statuses. Although FDA has plans for a new informatics system, it will make limited upgrades to DARRTS to improve its tracking and oversight of PMRs.

FDA implemented our third recommendation that called for FDA to determine the reasons some PMRs had been delayed and to take action as appropriate. Specifically, FDA determined that as of May 13, 2016, only one of the PMRs that we asked it to address was still delayed. FDA has been in contact with the sponsor of that delayed PMR and is in the process of resolving the delay.

For the full text of FDA's comments, see the Appendix.

APPENDIX A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

DATE: June 10, 2016

TO: Inspector General

FROM: Associate Commissioner for Public Health Strategy and Analysis

SUBJECT: FDA's Comments to OIG Draft Report, *FDA is Issuing More Postmarketing Requirements, but Challenges with Oversight Persist*, OEI-01-14-00390

FDA is providing the attached comments to the OIG Draft Report, *FDA is Issuing More Postmarketing Requirements, but Challenges with Oversight Persist*, OEI-01-14-00390.

We appreciate the opportunity to review and comment on this draft report before it is published.

Peter Lurie
Associate Commissioner for Public Health
Strategy and Analysis

Attachment

FDA's General Comments to
OIG's Draft Report: "FDA is Issuing More Postmarketing Requirements but Challenges with Oversight Persist" OEI-01-14-00390

FDA appreciates the opportunity to review and comment on OIG's draft report. The FDA is committed to robust oversight of drug safety, including oversight of postmarketing studies that provide additional important information about the safety and effectiveness of approved drugs. The Agency's responses to each of OIG's recommendations are below.

Recommendation 1
Standardize a form for ASRs, ensure that they are complete, and require sponsors to submit them electronically.

FDA concurs with the recommendation to standardize the format of Annual Status Reports (ASRs) for postmarketing requirements (PMRs) and commitments (PMCs).

Federal regulations specify what information should be included in the status report for each PMR and PMC (21 CFR 314.81(b)(2)(vii) for NDAs; and 601.70(b) for BLAs). However, the regulations do not specify the format in which this information should be submitted. FDA's guidance, *Reports on the Status of Postmarketing Study Commitments —Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*, provides recommendations for the format of the ASR, but this format is not required.

FDA is exploring mechanisms by which FDA may standardize the format for ASRs and require sponsors to submit them electronically. We anticipate that an FDA proposal concerning a standardized format for electronic submission of ASRs (and other annual report information) will issue by the end of calendar year (CY) 2017.

FDA has initiated revisions of MAPP 6004.2, Procedures for Completing and Processing the Form "Annual Status Report Review Form: PMR and PMC Summary," to ensure that staff responsible for reviewing ASR submissions consistently check that the content is complete, and follow up with sponsors to obtain missing information. Revisions to the MAPP should be finalized by the end of the second quarter of CY 2017. FDA has also revised the ASR review form used by staff to complete and document review of ASR submissions to clarify and improve the information to be collected from the ASR, as well as to facilitate entry of data from the completed review forms into DARRTS. These changes, together with a standardized ASR format, should ensure improve ASR submissions.

Recommendation 2
Build capacity in DARRTS to support PMR oversight.

FDA's General Comments to
OIG's Draft Report: "FDA is Issuing More Postmarketing Requirements but Challenges with Oversight Persist" OEI-01-14-00390

Automated reports from DARRTS on the status of ASRs could improve FDA staff's ability to identify pending ASR due dates, PMR statuses that are overdue for updates, or missing and late ASRs. To improve the utility of DARRTS for overseeing PMRs, FDA could:

- **Add reports to DARRTS for tracking ASRs and PMR statuses,**
- **Automate work processes to alert data entry staff that an ASR has been reviewed and should be entered into DARRTS, and**
- **Conduct routine quality assurance of DARRTS data to ensure completeness.**

FDA concurs with the recommendation to improve its informatics systems to better support oversight of PMRs.

Using data already available in DARRTS, FDA has already initiated efforts to make certain reports available as "standard" reports that can be generated independently by FDA staff (and not only by certain staff with select access to these data). For example, FDA has initiated efforts to make "standard" DARRTS reports available for ASRs and PMR/PMC Final Reports that have been received but not yet reviewed by FDA. These reports will facilitate the meeting of internal goal dates for review of ASR and PMR/PMC Final Report submissions, and therefore achieve more timely updating of PMR statuses in the database. FDA anticipates that these two reports will be available in DARRTS by the end of CY 2016. FDA will continue to develop and implement additional DARRTS "standard" reports as appropriate and feasible.

The Center for Drug Evaluation and Research (CDER) is transitioning from DARRTS to a new informatics system (the CDER Informatics Platform). During this transition, DARRTS is functioning as a legacy system with limited system upgrades. Nevertheless, FDA has implemented certain changes to DARRTS to facilitate more complete data capture for PMRs. These changes include the revision of a data field to specifically capture the PMR establishment date; specification that the field for describing the reason for the PMR status change is "mandatory;" and certain DARRTS screen enhancements that change views and refine fields in order to improve data entry by staff. Additionally, FDA has updated the Standard Operating Procedure (SOP) used by data entry staff to clarify or add new instructions about procedures for PMR data entry. Both the DARRTS system changes and changes to procedures for DARRTS data entry should improve FDA's tracking and oversight of PMRs. FDA plans to continue to make DARRTS system changes to the extent that these are feasible and necessary during the transition period.

FDA anticipates that the transition to the new Informatics Platform will be complete within the next 2-3 years. Automated PMR/PMC work processes are planned within the Informatics Platform that will alert CDER review staff about ASRs that have been received and reviewed,

and alert data entry staff about completed ASR reviews for which PMR status updates are required. Ideally, for more timely and accurate data updates, the new informatics system will also facilitate automated population of fields regarding PMR status, either based on incoming standardized ASR submissions, or completion of the ASR review.

FDA is exploring how it can conduct similar analyses related to quality assurance of DARRTS data that could be performed on a routine basis, using samples of data.

Recommendation 3

Determine the reasons that some PMRs have been delayed for years, and take action as appropriate.

We found that four PMRs have been delayed for 4 years, and four that have been delayed for 5 years. FDA should review these PMRs and its data to determine whether they are truly delayed, or if they only appear to be delayed because FDA has not updated the status of these PMRs in DARRTS. FDA should take actions appropriate to resolve these delayed PMRs.

FDA reviewed the current status of the eight (8) PMRs in the cohort evaluated by OIG that had been in delayed status for 4 or 5 years as of the end of FY2014. As of May 13, 2016, only one of these PMRs is still delayed. In greater detail, 4 of these PMRs have been fulfilled, 2 PMRs have been released, 1 PMR is in submitted status, and 1 PMR is still delayed. The delayed PMR is a PREA PMR for which the sponsor's request for deferral extension (i.e., extension of the deferred Final Report submission date) was denied by FDA. The sponsor was notified that they are out of compliance with the PREA requirements, and instructed to provide the Agency with the reason(s) for the delayed pediatric assessment and a date by which they expected to submit the assessment. The sponsor has since responded, and FDA discussions with the sponsor about the conduct of the study are continuing.

FDA's review of the final report for the PMR in "submitted" status is ongoing. The goal for FDA review of reports of postmarketing studies and trials is 1 year from the date of receipt of the report and that timeframe has not yet elapsed.

Consequently, to date, FDA has taken action to resolve all of the 8 PMRs in the cohort that OIG identified as delayed for 4 or 5 years as of the end of FY 2014.

ACKNOWLEDGMENTS

This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Russell Hereford, Deputy Regional Inspector General.

Jessica Fargnoli served as the team leader for this study, and Elizabeth Havener served as the lead analyst. Central office staff who provided support include Meghan Kearns and Joanne Legomsky.

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