

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**FDA'S MONITORING OF
POSTMARKETING STUDY
COMMITMENTS**



Daniel R. Levinson
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OBJECTIVES

1. To determine the extent to which new drug applications involve postmarketing study commitments with the Food and Drug Administration (FDA).
2. To determine how and the extent to which FDA monitors open postmarketing study commitments for new drug applications.

BACKGROUND

FDA requires all new drugs to undergo clinical testing to demonstrate their safety and efficacy prior to approval for sale in the United States. However, these premarket clinical trials involve relatively small numbers of individuals compared to the actual numbers who will eventually use the drugs. Therefore, it is possible that additional information regarding the safe and effective use of any drug may not be fully known until the drug is approved and prescribed to larger numbers of individuals in the general population. To learn more about the risks, benefits, and optimal use of an approved drug, drug applicants may conduct postmarketing studies, which are studies conducted while drugs are already on the market. These studies have become increasingly common in recent years. Meanwhile, members of Congress, FDA, and others have raised concerns that drug applicants are not completing these studies in a timely manner.

FDA has the authority to require postmarketing study commitments in certain situations (e.g., accelerated approval), but most postmarketing study commitments are requested by FDA and agreed to by drug applicants. The Food and Drug Administration Modernization Act of 1997 (FDAMA) provided FDA with new authorities for monitoring certain types of postmarketing studies. FDAMA requires that drug applicants submit annual status reports (ASRs) that provide information on the status of certain postmarketing studies. Some of the information from these reports is considered public information. Reviewers within FDA's Center for Drug Evaluation and Research (CDER) are charged with validating the accuracy of these reports.

We reviewed FDA's database of postmarketing study commitments for new drug applications approved during fiscal years 1990 through 2004. We also examined documents regarding postmarketing study commitments that drug applicants submitted to FDA in fiscal year

2004. We interviewed project managers in CDER. Finally, we reviewed FDA policies and procedures regarding postmarketing commitments.

EXTENT OF COMMITMENTS

Forty-eight percent of new drug applications approved from fiscal years 1990 through 2004 involved at least one postmarketing study commitment.

FDA classified 74 percent of these postmarketing study commitments as clinical studies. Ninety-one percent of postmarketing commitments were requested by FDA and agreed to by drug applicants as opposed to being required by statute or regulation.

Approved new molecular entities tended to have more postmarketing study commitments than other approved new drug applications.

Two of fifteen review divisions at FDA accounted for 40 percent of the postmarketing study commitments from fiscal years 1990 through 2004.

FINDING

FDA cannot readily identify whether or how timely postmarketing study commitments are progressing toward completion.

About one-third of ASRs were missing or incomplete.

- Thirty-five percent of the 336 ASRs that were or should have been submitted in fiscal year 2004 were missing entirely or contained no information on open postmarketing study commitments. Thirty-nine percent were missing one or more items of required information.

ASRs contain information of limited utility.

- Even complete ASRs lack information that would be useful in monitoring the progress of postmarketing study commitments.
- FDA has limited recourse when drug applicants do not submit required information or do not demonstrate progress in completing their postmarketing study commitments.

FDA lacks an effective management information system for monitoring postmarketing study commitments.

- FDA reviewers cannot easily identify which annual reports should include ASRs for outstanding postmarketing study commitments.

- FDA utilizes a confusing numbering system to identify postmarketing study commitments, and drug applicants do not always provide numbers for commitments they address in ASRs.
- FDA frequently does not populate the fields of its database of postmarketing study commitments with information from commitment letters and ASRs that could assist reviewers in tracking the progress of commitments.

Monitoring postmarketing study commitments is not a top priority at FDA.

- FDA reviewers indicated to us that monitoring postmarketing study commitments is not generally considered a top priority at FDA. Our analysis showed that FDA validated only 30 percent of ASRs submitted in fiscal year 2004; five review divisions did not validate any ASRs.

RECOMMENDATIONS

To better determine whether and how timely postmarketing study commitments are progressing toward completion, FDA should:

- Instruct drug applicants to provide additional, meaningful information in their ASRs;
- Improve the management information system for monitoring postmarketing study commitments so that it provides timely, accurate, and useful information; and
- Ensure that postmarketing study commitments are being monitored and that ASRs are being validated.

AGENCY COMMENTS

FDA disagreed with our finding that it cannot readily identify whether and how timely postmarketing study commitments are progressing toward completion. The agency emphasized both the seriousness with which it takes its obligation to monitor the progress of postmarketing study commitments and that it makes some information regarding the commitments publicly available.

FDA concurred with two of our three recommendations. Specifically, FDA agreed with our recommendations to improve the management information system for monitoring postmarketing study commitments and to ensure that postmarketing study commitments are being monitored and ASRs are validated. The agency highlighted ongoing

efforts to enhance its postmarketing study commitment database and reporting capabilities, train its review division staff on ASR validation procedures, and standardize the process by which postmarketing study commitments are requested and reviewed.

FDA disagreed with our recommendation that it instruct drug applicants to provide additional, meaningful information in their ASRs, citing that implementing such a recommendation would require new regulations.

OFFICE OF INSPECTOR GENERAL RESPONSE

In disagreeing with our finding, FDA highlighted several areas in which it has made improvements. We appreciate that FDA has taken steps to improve its monitoring of postmarketing study commitments. However, our review of the postmarketing study commitment database and annual status reports, as well as our interviews with agency officials, demonstrated that FDA cannot readily identify whether or how timely postmarketing study commitments are progressing toward completion for the period of our review.

We recognize that our recommendation that FDA instruct drug applicants to provide additional, meaningful information in their ASRs could require regulatory changes. In response, we added language to our recommendation acknowledging that FDA may need to seek regulatory changes to improve its system for monitoring postmarketing study commitments.

We also made other minor changes to our report based on FDA's technical comments.

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OBJECTIVES

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2. To determine how and the extent to which FDA monitors open postmarketing study commitments for new drug applications.

BACKGROUND

The Importance of Postmarketing Studies

FDA requires all new drugs to undergo clinical testing to demonstrate their safety and efficacy prior to approval for sale in the United States.¹ However, these premarket clinical trials involve relatively small numbers of individuals compared to the actual numbers who will eventually use the drugs. Therefore, it is possible that additional information regarding the safe and effective use of any drug may not be fully known until the drug has been approved and then prescribed to larger numbers of individuals in the general population. It is especially likely that information regarding rare side effects will not be fully known based on premarket trials.

To learn more about the risks, benefits, and optimal use of an approved drug, drug applicants may conduct additional studies after a drug is already on the market.² These studies, known as postmarketing studies, may evaluate a drug's safety, efficacy, pharmacology, toxicology, and/or manufacturing controls, among other factors. It is common for a drug to be involved in multiple postmarketing studies.

Although postmarketing studies provide important information about drugs, FDA does not consider them essential to drug approvals except in limited circumstances, such as to support accelerated approval applications or for required pediatric studies.³ Based on the results of postmarketing studies, FDA may approve changes to a drug's label, approve a drug for new uses, require changes in a drug's manufacturing process, or, in rare cases, seek to withdraw a drug from the market. Most postmarketing studies provide information that leads to labeling changes, such as how optimal dosing may differ across patient populations.

Given the valuable information that postmarketing studies can provide, it is not surprising that they are becoming increasingly common.

A 1996 Office of Inspector General (OIG) report found that the percentage of new drugs with postmarketing study commitments increased from the early 1970s through the early 1990s.⁴ FDA's report to Congress on postmarketing study commitments in April 2002 found a similar trend.⁵

At the same time, members of Congress, FDA, and others have raised concerns that drug applicants are not fulfilling their postmarketing study commitments in a timely manner.^{6,7}

Types of Postmarketing Studies

There are three main types of postmarketing studies: (1) studies required by FDA, (2) studies requested by FDA and agreed to by drug applicants, and (3) voluntary studies. The latter two are the most common types of postmarketing studies.

Studies required by FDA. In certain situations, FDA has the statutory or regulatory authority to require drug applicants to conduct postmarketing studies.⁸ These postmarketing study commitments are the least common.

Studies requested by FDA and agreed to by drug applicants. Although FDA can request that drug applicants conduct postmarketing studies at any time, most requests for postmarketing studies are made prior to drug approval, when FDA has leverage over drug applicants who are eager to obtain approval for their products. Manufacturers not only agree to these commitments in writing, but FDA also lists the commitments in final approval letters. However, FDA does not have any authority to sanction drug applicants that fail to conduct these studies. These are the most common postmarketing study commitments.

Voluntary studies. Voluntary studies are studies that drug applicants conduct on their own initiative.

FDA's Monitoring of Postmarketing Study Commitments

Section 130(a) of Title I of the Food and Drug Administration Modernization Act of 1997 (FDAMA) added section 506B to the Food, Drug, and Cosmetic Act and provided FDA with new authorities for monitoring certain postmarketing studies associated with drugs and biologics.⁹ Congress enacted this section in response to concerns expressed by FDA and the public about the timeliness with which postmarketing studies were being completed and the need to update drug labeling with information obtained from such studies.¹⁰ Section 506B of FDAMA contains two particularly relevant provisions:

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(1) it requires reporting on the status of certain postmarketing studies, and (2) it establishes that certain information in these reports is considered public information.^{11,12} These reports, known as annual status reports (ASRs), are intended to be a key tool for FDA to use in monitoring postmarketing study commitments.

In October 2000, FDA issued final regulations on the nature and contents of ASRs for open postmarketing study commitments required under FDAMA.¹³ Pursuant to the regulations, the types of commitments for which drug applicants must submit ASRs are studies that address: (1) clinical safety, (2) clinical efficacy, (3) clinical pharmacology, and (4) nonclinical pharmacology.¹⁴ This requirement covers all studies required by FDA and all studies requested by FDA and agreed to by drug applicants, except for chemistry, manufacturing, and control studies.¹⁵ The requirement excludes voluntary studies.

Throughout this report, we use the terms commitment and postmarketing study commitment to refer only to postmarketing studies that require annual reporting under FDAMA.

Pursuant to regulation, ASRs must contain the following information:¹⁶

- Applicant name
- Product name
- Application number
- Date of U.S. approval
- Date of postmarketing study commitment
- Description of postmarketing study commitment
- Schedule for completion of and reporting on the postmarketing commitment
- Status of the commitment
 - Pending: The study has not started, but is not behind schedule.
 - Ongoing: The study is ahead of or on schedule.
 - Delayed: The study is behind the original schedule.
 - Terminated: The study was ended before completion, but a final report has not been submitted to FDA.

- Submitted: The study was completed or terminated and a final report was submitted to FDA for review.
- Explanation of the status of the study

Drug applicants must submit ASRs within 60 days of the anniversary of the approval of a new drug application.¹⁷ Generally, ASRs can be found in larger reports, known as annual reports, which are submitted by drug applicants and contain information concerning changes in manufacturing practices and labeling, among other things. FDA's goal is to review ASRs within 90 days of receipt.¹⁸ The main focus of FDA reviews is to validate the accuracy of the information in the ASRs; however, FDA also determines whether drug applicants are making adequate progress toward fulfilling their commitments. FDA may follow up with drug applicants regarding these reports as necessary, such as for late and/or incomplete reports.

In April 2001, FDA issued draft guidance to industry that elaborates on the regulatory requirements for the content of ASRs.¹⁹ This guidance was finalized in February 2006 (after the period of our review).²⁰

The Prescription Drug User Fee Act of 2002, which reauthorized user fees for the review of new drug applications, also provided FDA with additional tools to improve compliance with postmarketing commitments. The law amended section 506B of the Federal Food, Drug, and Cosmetic Act to require the Secretary to inform the public if and when drug applicants fail to fulfill such commitments.²¹ In November 2004, FDA announced that it had contracted with the Institute of Medicine to study the effectiveness of the drug safety system with an emphasis on the postmarket phase.²² In February 2005, FDA announced the creation of the Drug Safety Board to oversee drug safety issues, in which postmarketing studies can play a part.²³

Center for Drug Evaluation and Research Procedures

Within FDA, the Center for Drug Evaluation and Research (CDER) is responsible for reviewing new drug applications and for monitoring postmarketing study commitments for drugs. Reviewers within CDER's Office of New Drugs (OND) have the lead responsibility for reviewing new drug applications and ASRs for postmarketing study commitments. Typically, the reviewer who reviewed a new drug application also reviews any associated ASRs. CDER reviewers have backgrounds in various disciplines, including pharmacy, chemistry, and medicine, among others. There are multiple review divisions within OND.

In 1996, CDER issued procedures for tracking and monitoring postmarketing commitments.²⁴ CDER is in the process of updating these procedures. In 2001, CDER implemented a new database to track and monitor the status of postmarketing commitments. To foster public accountability in completing these commitments, portions of this database are available to the public on the FDA Web site.²⁵

In March 2005, CDER issued procedures for reviewing ASRs for postmarketing study commitments. These procedures require reviewers to complete worksheets that document that they verified the accuracy of the information in the ASRs. Reviewers must indicate on the worksheets whether they agree with the status of commitments and explanations of status as reported by drug applicants.²⁶

After a final study report is submitted, CDER procedure calls for a review to determine whether a given commitment has been fulfilled; if it has, CDER sends a fulfillment letter to the drug applicant.²⁷

Prior Office of Inspector General Reports

In May 1996, OIG issued a report assessing the effectiveness of FDA's monitoring of postmarketing study commitments for drugs.²⁸ This inspection found that the number of new drugs with postmarketing commitments was increasing, but that FDA lacked both formal procedures for monitoring these commitments and an effective management tool to track the status of commitments. The inspection attributed these vulnerabilities to competing priorities, limited resources, and an inability to enforce compliance.

In March 2003, OIG issued a report assessing how FDA manages the new drug application review process.²⁹ This inspection found that reviewers were often uncertain about what types of postmarketing commitments to request of drug applicants prior to drug approval.

Recent FDA Initiatives

Over the past several years, FDA has changed the way it monitors postmarketing study commitments. FDA has: (1) implemented a new database to track the status of postmarketing study commitments, (2) issued new procedures for tracking and reviewing commitments, (3) received additional authorities to require drug applicants to report annually on the progress of their commitments and publicly disclose information from these reports, (4) issued new procedures for reviewing annual status reports, and (5) issued guidance for industry regarding status reports for postmarketing study commitments.

METHODOLOGY

Our analysis involved several data sources and methods. (For a complete description of our methodology, see Appendix A.)

We reviewed FDA's database of postmarketing study commitments for new drug applications approved from fiscal years 1990 through 2004. Because the database does not consistently show when postmarketing study commitments were initiated, we linked each postmarketing study commitment to the fiscal year in which its new drug application was approved. We performed trend analyses by year, study type, study category, review division, and study status. We conducted the same trend analyses for postmarketing study commitments associated with new molecular entities (NMEs), a subset of new drug applications for drugs that contain active ingredients never before approved for marketing in the United States.

We reviewed annual reports that FDA received from drug applicants in fiscal year 2004 that did or should have contained ASRs for open postmarketing study commitments. We matched the postmarketing studies listed in these ASRs to commitments in FDA's database of postmarketing study commitments and analyzed the ASRs for completeness and accuracy. We also reviewed all available FDA validations and other supporting documentation associated with fiscal year 2004 ASRs.

We also reviewed all fulfillment letters issued by FDA in fiscal year 2004. For a subset of commitments fulfilled in fiscal year 2004, we obtained additional documentation from FDA, which we reviewed to determine reasons for lateness and the extent of FDA followup.

We interviewed project managers at 14 of the 16 review divisions within CDER. We did not speak to reviewers at the two divisions that oversee therapeutic biologic drugs, which were excluded from the scope of this inspection.³⁰ We used a structured questionnaire to conduct the interviews; this questionnaire addressed policies and procedures, challenges, and recommendations regarding monitoring postmarketing study commitments. We conducted all interviews by telephone.

Finally, we reviewed all relevant policies, procedures, and guidance documents for postmarketing study commitments issued by FDA. We used these documents to better understand the process for monitoring postmarketing study commitments.

I N T R O D U C T I O N

We conducted this evaluation in accordance with the “Quality Standards for Inspections” issued by the President’s Council on Integrity and Efficiency and the Executive Council on Integrity and Efficiency.

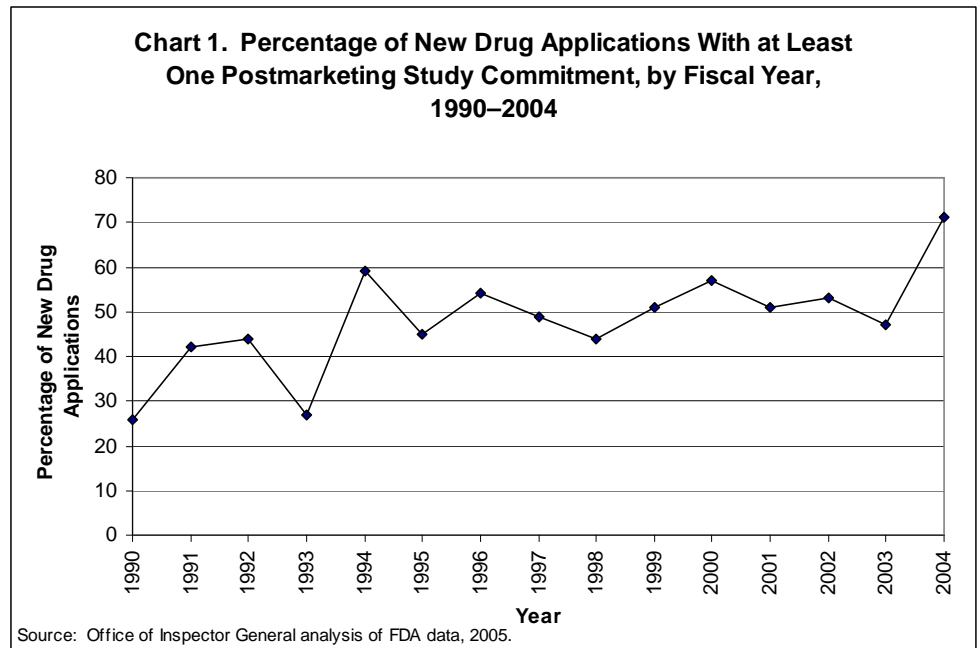


E X T E N T O F C O M M I T M E N T S

In this section we provide a summary of the extent and nature of postmarketing study commitments associated with new drug applications approved from fiscal years 1990 through 2004. For additional information, see Appendix B.

Forty-eight percent of new drug applications approved from fiscal years 1990 through 2004 involved at least one postmarketing study commitment.

On an annual basis, the percentage of approved new drug applications with at least one commitment ranged from a low of 26 percent (in 1990) to a high of 71 percent (in 2004). From fiscal years 1995 through 2003, the percentage of approved new drug applications with at least one commitment was fairly constant. (See Chart 1 below.)



FDA classified 74 percent of postmarketing study commitments from fiscal years 1990 through 2004 as clinical. Ninety-one percent of postmarketing commitments were requested by FDA and agreed to by drug applicants as opposed to being required.

Clinical postmarketing studies involve an approved drug being administered to humans and evaluated for safety and/or efficacy. (See Table 1 on the following page.)

E X T E N T O F C O M M I T M E N T S

Table 1. Postmarketing Study Commitments by Nature From Fiscal Years 1990–2004

Nature of Postmarketing Study Commitment	Number of Postmarketing Study Commitments	Percentage of Postmarketing Study Commitments
Clinical	1,732	74
Pediatric*	326	14
Nonclinical	255	11
All Others	40	2
Total	2,353	**

*Pediatric studies are considered clinical studies, but are tracked separately in FDA's database.

** Column does not sum to 100 due to rounding.

Source: Office of Inspector General analysis of FDA data, 2005.

Further, the overwhelming majority of postmarketing study commitments from the period of our review were requested by FDA. (See Table 2 below.) Drug applicants agree to conduct requested study commitments in writing, and FDA lists the commitments in final approval letters.

Table 2. Postmarketing Study Commitments by Type From Fiscal Years 1990–2004

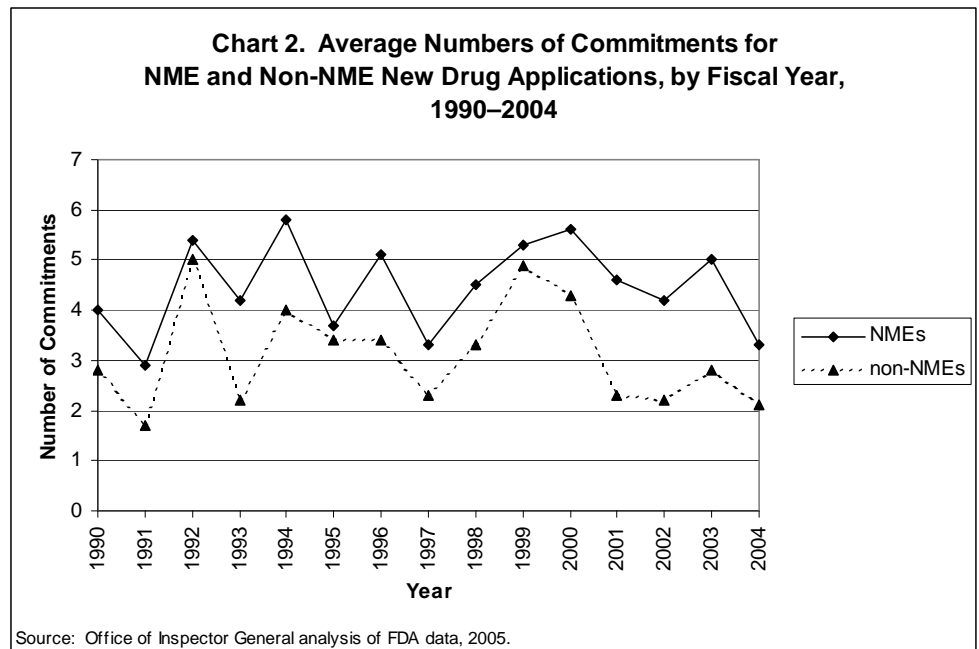
Type of Postmarketing Study Commitment	Number of Postmarketing Study Commitments	Percentage of Postmarketing Study Commitments
Requested by FDA	2,132	91
Accelerated Approval*	118	5
Deferred Pediatric*	102	4
Animal Efficacy*	1	< 1
Total	2,353	100

* Full explanations of these postmarketing study commitment types can be found in endnote 8.

Source: Office of Inspector General analysis of FDA data, 2005.

Approved new molecular entities tended to have more postmarketing study commitments than other approved new drug applications.

NMEs are approved drugs that contain active ingredients that have never been approved for marketing in the United States. Because less is known about these entirely new drugs, it is perhaps not surprising that, on average, NMEs tended to be associated with more postmarketing study commitments than other new drug applications. (See Chart 2 below.)



Two of fifteen review divisions within CDER accounted for 40 percent of the postmarketing study commitments from fiscal years 1990 through 2004.

During the period of our inquiry, the Division of Anti-Viral Drug Products oversaw 26 percent of the postmarketing study commitments and the Division of Special Pathogen and Immunologic Drug Products oversaw 14 percent of postmarketing study commitments. None of the other CDER review divisions oversaw more than 10 percent of postmarketing study commitments. (See Appendix B, Table 2, for additional information.)

► FINDING

FDA cannot readily identify whether or how timely postmarketing study commitments are progressing toward completion

About one-third of ASRs were missing or incomplete

ASRs are intended to be a key source of information for FDA and an important tool for monitoring postmarketing study commitments.

Of the 336 ASRs that, according to FDA, were or should have been submitted by drug applicants in fiscal year 2004, 35 percent (119) were either missing entirely or contained no information on open postmarketing study commitments; some stated explicitly that no open postmarketing study commitments existed when, in fact, they did. (See Table 3 below.)

Table 3. Classification of ASRs That Were or Should Have Been Submitted in Fiscal Year 2004

Description of ASR	Number of ASRs	Percentage of ASRs
ASR Not Submitted by Drug Applicant	27	8
ASR Did Not Contain Information on Open Postmarketing Study Commitments	92	27
ASR Contained Information on at Least One, but Not Necessarily All Open Postmarketing Study Commitments	217	65
Total	336	100

Source: Office of Inspector General analysis of FDA data, 2005.

Of the 788 commitments listed in the ASRs from fiscal year 2004 that could be matched with commitments in FDA’s database of postmarketing study commitments, 39 percent (307) were missing one or more items of required information. (See Table 4 on the following page.) For example, drug applicants did not provide a status for 8 percent of commitments (65) and did not provide an explanation of

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status for 10 percent of commitments (78). (See Appendix B, Table 3, for additional information.)

For an additional 14 percent of commitments (110), drug applicants wrote something about the status of their commitments but did not provide one of the status definitions (i.e., pending, ongoing, delayed, terminated, and submitted) that are required by regulation.³¹ For example, we reviewed ASRs that identified the status of commitments as “the final report of the study will be available by the end of the year,” and “the data is currently being analyzed.” If drug applicants do not provide one of the standard status definitions, FDA may not be able to post accurate information about the status of commitments on its public Web site of postmarketing study commitments.

Table 4. Number of Required Elements Missing From Fiscal Year 2004 ASRs, per Postmarketing Study Commitment

Number of Missing Elements	Number of Postmarketing Study Commitments	Percentage of Postmarketing Study Commitments
7	1	< 1
6	3	< 1
5	9	1
4	49	6
3	54	7
2	68	9
1	123	16
0	481	61
Total	788	100

Source: Office of Inspector General analysis of FDA data, 2005.

ASRs contain information of limited utility

Even complete ASRs often lacked information that would be useful in monitoring the progress of postmarketing study commitments. Of the FDA officials we interviewed at the 14 review divisions, officials at 9 told us that the inadequacy of information even on complete ASRs poses a major or moderate challenge to their ability to effectively

monitor the progress of postmarketing study commitments. Some of the FDA reviewers we interviewed indicated that the information provided on ASRs does not assist in ensuring progress of postmarketing study commitments. For example, one official we interviewed categorized the current process for monitoring postmarketing study commitments as “very shallow” because, although validating ASRs provides information on whether FDA agrees with the status of commitments, it does not necessarily serve to move commitments toward completion.

In 2001, FDA released draft guidance to industry on how to complete ASRs for postmarketing study commitments.³² This guidance, finalized in February 2006, reiterates and provides additional detail about the regulatory requirements. It includes a section on the content and format of ASRs and provides detailed information on the nine required items of information that, pursuant to regulations, must be reported for each open postmarketing study commitment.

Nine elements required to be reported on ASRs for open postmarketing study commitments

- Applicant name
- Product name
- Application number
- Date of U.S. approval
- Date of postmarketing study commitment
- Description of postmarketing study commitment
- Original schedule for completing the postmarketing study commitment
- Status of the commitment
- Explanation of the status

Source: 21 CFR § 314.81(b)(2)(vii).

(See the box to the right.) The regulations require drug applicants to report a schedule for completion and reporting of the postmarketing study commitment. The regulations also recommend that the schedule contain certain milestones, including projected dates of initiation for different phases of the studies. FDA recognizes these milestones and others—including dates of submission of study protocols, completion of participant enrollment, completion of the study, and submission of the final study report—as “common and important to determining study progress.”³³ Additionally, the guidance states that in providing an explanation of any commitment’s status, a drug applicant should briefly explain the progress of the commitment with regard to its original schedule.³⁴

Our review of ASRs found that they frequently lacked the information and detail either required or recommended by regulation. For example, many of the ASRs we reviewed provided none of the milestone dates recommended by the regulations, and others included information on only some of the dates. Further, even when drug applicants explained

the status of commitments, the explanations often lacked detail. We saw examples of drug applicants simply listing the status of the commitment (e.g., pending) as both the status and the explanation of the status.

The inadequacy of information on ASRs makes it difficult for FDA reviewers to readily identify the data they actually require to monitor the progress of postmarketing study commitments effectively. Not only are the most substantive aspects of the ASRs often lacking detail, but further, ASRs do not give reviewers complete pictures of the progress of postmarketing study commitments. Rather, reviewers must evaluate additional reports—including study protocols, progress reports, and final reports—submitted by drug applicants over the past year(s).

However, ASRs do not include information that would link commitments with those reports. FDA does not require drug applicants to include in ASRs the dates on which they submitted additional information or to where they submitted that information. Officials told us that having this information readily available would make it easier to locate the documents they need to review. One official said that, currently, finding the information necessary to review open postmarketing study commitments is like “looking for a needle in a haystack.”

Section 130(a) of Title 1 of FDAMA does not provide any enforcement authority to FDA for instances in which drug applicants do not submit required information or demonstrate progress in completing their postmarketing study commitments. As a practical matter, FDA officials have two options for short-term action in such cases: (1) sending letters and (2) placing phone calls to drug applicants. Although many of the FDA officials we interviewed stated that letters or phone calls may often be enough to get drug applicants to submit the information FDA is requesting, in some cases these options are ineffective.

FDA lacks an effective management information system for monitoring postmarketing study commitments

Difficulty identifying overdue ASRs. Although FDA management provides review divisions with some reports for monitoring the status of postmarketing study commitments, there appears to be a low level of awareness of these reports in the review divisions and the reports may be of limited utility. The FDA officials we interviewed in the review divisions indicated that they cannot readily identify which annual

reports have associated open postmarketing commitments and, therefore, should contain ASRs. The reviewers we interviewed told us that they must either cross-reference the postmarketing commitment database for open postmarketing study commitments or rely on informal tools (e.g., knowledge of FDA employees or informal lists) to determine whether an approved new drug application has open postmarketing commitments requiring the submission of an ASR. Several FDA officials we interviewed stated that they only know reports will be late when drug applicants call to tell them. Of the FDA officials we interviewed at the 14 review divisions, officials at 8 stated that the current tracking system poses either a major or moderate challenge to their ability to effectively monitor the progress of postmarketing study commitments.

Our review of ASRs uncovered additional barriers to using the postmarketing study commitment database to determine when ASRs are overdue. We compared the list of ASRs FDA reported as having been submitted or not submitted in fiscal year 2004 with the database of postmarketing study commitments. This comparison showed that not all of the open commitments in the database were accounted for in ASRs.³⁵ FDA reported that some of these commitments were for drugs that had been withdrawn from the market; yet the database did not capture this information. Further, FDA reported that some commitments were not reported on because of drug applicant mergers or other reasons. Nonetheless, the regulations require that ASRs be submitted annually until a final study report has been submitted to FDA and the drug applicant has been notified that the study commitment has been fulfilled.³⁶ The regulations provide no exceptions for drug applications that have experienced changes in ownership.

Confusing numbering system. FDA uses a confusing numbering system for postmarketing study commitments. At the time of a drug's approval, FDA numbers any commitments for that drug sequentially starting with "1." In addition, when FDA approves a subsequent supplemental application for the same drug, it again numbers any commitments sequentially starting with "1." These numbers appear in the drug approval letters sent to drug applicants and in FDA's database of postmarketing study commitments.

Further complicating matters is that drug applicants do not always number the commitments they address in their ASRs; even when they do so, the numbers do not always match the numbers in FDA's database

of postmarketing study commitments. As commitments are fulfilled, drug applicants may renumber remaining commitments, so that if commitments “1” and “2” are fulfilled, a drug applicant may list the original commitment “3” as commitment “1” in an ASR.

We observed that the commitment numbers and descriptions used in ASRs did not always match the commitment numbers and descriptions in the FDA database. In addition, we saw examples of FDA using different commitment numbers in its validations of ASRs than it used in the database of postmarketing study commitments. Having to cross-reference multiple sources to determine the correct identifiers for postmarketing study commitments adds to the already burdensome task of tracking postmarketing study commitments.

FDA has recently adopted new procedures to minimize confusion regarding how to number postmarketing study commitments. However, this new process still relies on drug applicants to number commitments consistently over time.

Database inconsistently populated. FDA frequently does not populate the fields of its database of postmarketing study commitments with information from commitment letters and ASRs that could assist reviewers in tracking the progress of commitments. We observed that database fields that should contain protocol submission dates, original projected completion dates, study start dates, and current projected completion dates are not always populated. For example, out of a total of 2,353 commitments in the database, study start dates were present for only 6 percent (132) and original projected completion dates were present for only 21 percent (484). Without this information readily available, it is difficult for reviewers to determine whether studies are on schedule. In addition, FDA generally does not record in its database the dates on which drug applicants make final report submissions; only 3 percent of commitments classified by FDA as “fulfilled” in the database listed the final report submission date. Without this information, it is not possible to readily determine the length of time it takes for drug applicants to complete postmarketing study commitments or whether they are being completed at all.

To determine whether drug applicants are completing their postmarketing study commitments early, on time, or late, we attempted to analyze postmarketing study commitments deemed by FDA to have been fulfilled in fiscal year 2004.³⁷ Because of missing data, we were able to determine the timeliness of only 18 of the 145 commitments

fulfilled in fiscal year 2004.³⁸ Of these 18 commitments, 3 were completed on time or early; the other 15 were completed, on average, about 5 months late.

According to FDA officials, commitments that predated FDAMA and the 2001 reporting regulations may not have had study schedules established at the time of approval and, therefore, would not necessarily have commitment schedule dates within the database. We observed that the prevalence of commitment schedule dates in the database has improved since the 2001 reporting regulations were enacted. However, the regulations called for all commitments, including those that predate FDAMA, to submit ASRs that included schedules.³⁹

Because the database of postmarketing study commitments is not populated with these dates, the public Web site on postmarketing study commitments may not keep the public and the medical community informed of the status of postmarketing obligations.

Monitoring postmarketing study commitments is not a top priority at FDA

Of the FDA officials we interviewed at the 14 review divisions, officials at 9 said that the current priority of monitoring postmarketing study commitments poses a major or moderate challenge to their ability to effectively monitor the progress of the studies. FDA officials told us that, among other things, reviewing drug applications and documenting FDA/industry meetings are higher priorities than reviewing postmarketing study commitments and ASRs. Further, central OND management provides project managers with regular updates on upcoming Prescription Drug User Fee Act goals and other priority items; however, no centrally generated report addresses postmarketing study commitments and their progress toward completion. Many of the FDA officials we interviewed told us that when they prioritize their workloads, they simply lack the resources to accomplish all of the tasks assigned to them.

FDA validated only 30 percent (65) of the 217 ASRs that were actually submitted by drug applicants in fiscal year 2004 and included at least one open postmarketing study commitment. Five review divisions did not validate any of the ASRs they were charged with overseeing in fiscal year 2004. Further, even when ASRs were validated, FDA frequently did not meet its goal of completing ASR reviews within 90 days of receipt and often appeared to fall short of meeting FDA requirements for monitoring postmarketing study commitments. (See Appendix B, Table 4, for additional information.) For example, we observed that

FDA reviewers sometimes agreed with drug applicants even when the applicants failed to provide one of the status options required by the regulations.

We recognize that FDA reviewers have multiple priorities in addition to monitoring postmarketing study commitments and that FDA faces limited staffing resources. We also recognize that FDA has taken steps to improve its monitoring system for postmarketing study commitments and has other initiatives underway. For example, in March 2005, FDA finalized an internal manual of policies and procedures regarding postmarketing study commitments and ASRs.⁴⁰ FDA is also in the process of redesigning its database of postmarketing study commitments and enhancing the postmarketing study commitment reporting system to make monitoring more efficient.

Postmarketing studies are important tools for gathering information about the risks, benefits, and optimal uses of drugs that may not be fully known until the drugs are approved and prescribed in the general population. Yet, we have identified shortcomings in the extent to which information is reported, the utility of the information that is collected, and the effectiveness of the current management information system. Taken together, these vulnerabilities raise concerns that FDA's tools for monitoring postmarketing study commitments—ASRs and its management information system—may not ensure that postmarketing study commitments are progressing toward completion.

Based on our review, we believe that FDA should take additional steps to improve the system for monitoring postmarketing study commitments so as to be able to readily identify whether and how timely postmarketing study commitments are progressing toward completion. Toward that end, we recommend that FDA:

Instruct Drug Applicants to Provide Additional, Meaningful Information in Their ASRs

FDA should instruct drug applicants to provide in their ASRs when and where they submitted reports on their open postmarketing study commitments. FDA officials must review these other reports to determine the progress of commitments.

While the regulations currently require drug applicants to report a schedule for completion and reporting of the postmarketing study commitment, they recommend but do not require that applicants provide in their ASRs relevant dates of key milestones. Such milestones could include: (1) submissions of study protocols, (2) completion of participant enrollment, (3) completion of studies, and (4) submissions of

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final reports. Toward this end, FDA may want to seek regulatory change to require a greater a level of detail in ASRs.

Improve the Management Information System for Monitoring Postmarketing Study Commitments So That It Provides Timely, Accurate, and Useful Information

FDA should take several steps to improve its management information system:

- o Ensure that commitments are numbered uniquely and logically.

The current numbering of postmarketing study commitments can create confusion and lead to misidentifying commitments. An effective numbering system would assign a unique identifier at the time of approval. FDA could then instruct drug applicants to use those unique identifiers on any submissions made to the agency, and FDA could use the identifiers in its management information system and on all correspondence regarding postmarketing study commitments.

- o Ensure that the database is populated with useful information.

Some information on postmarketing study commitments is already entered into FDA's database. FDA should also populate its database with, at a minimum, the following items: (1) study start dates, (2) original scheduled completion dates, and (3) final report submission dates.

Further, FDA should consider populating the database with additional information, including: (1) references to reports submitted by drug applicants, (2) numbers of participants enrolled while commitments are "ongoing," and (3) information pertaining to why commitments are "delayed," whenever applicable.

- o Enhance the current reporting capability that identifies late ASRs and outstanding commitments.

There appears to be a low level of awareness within the review divisions of the reports that identify late ASRs and outstanding commitments. Furthermore, these reports may be of limited utility. An enhanced management information system could generate reports that would enable reviewers to readily identify approved new drug applications for which ASRs are due as well as those with open commitments that are behind schedule.

Ensure That Postmarketing Study Commitments Are Being Monitored and That ASRs Are Being Validated

FDA must ensure that reviewers are meeting their oversight responsibilities for postmarketing study commitments. Although FDA faces competing priorities and limited staffing resources, ensuring that postmarketing studies are being completed in a timely manner is crucial to ensuring that the public and the medical community are aware of the risks, benefits, and optimal uses of approved drugs. To this end, FDA must ensure that reviewers have the information, tools, and time they need to complete this important task.

FDA should also consider seeking authority to obtain additional recourse options in cases of postmarketing study commitments that lag far behind schedule or for which required documents are not submitted. Currently, short of withdrawing a drug from the market—a remedy available to FDA only in limited circumstances—the only short-term, practical options available to FDA in dealing with drug applicants that do not comply with the terms of their commitments are sending letters and placing phone calls. Providing FDA reviewers with additional tools, such as the ability to impose monetary fines, may send a signal to drug applicants that there are consequences when postmarketing study commitments are not fulfilled.

AGENCY COMMENTS

FDA disagreed with our finding that it cannot readily identify whether and how timely postmarketing study commitments are progressing toward completion. The agency emphasized both the seriousness with which it takes its obligation to monitor the progress of postmarketing study commitments and that it makes some information regarding the commitments publicly available.

FDA concurred with two of our three recommendations. Specifically, FDA agreed with our recommendations to improve the management information system for monitoring postmarketing study commitments and to ensure that postmarketing study commitments are being monitored and ASRs are validated. The agency highlighted ongoing efforts to enhance its postmarketing study commitment database and reporting capabilities, train its review division staff on ASR validation procedures, and standardize the process by which postmarketing study commitments are requested and reviewed.

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FDA disagreed with our recommendation that it instruct drug applicants to provide additional, meaningful information in their ASRs, stating that implementing such a recommendation would require new regulations.

See Appendix C for complete agency comments.

OFFICE OF INSPECTOR GENERAL RESPONSE

In disagreeing with our finding, FDA highlighted several areas in which it has made improvements. We appreciate that FDA has taken steps to improve its monitoring of postmarketing study commitments. However, our review of the postmarketing study commitment database and annual status reports, as well as our interviews with agency officials, demonstrated that FDA cannot readily identify whether or how timely postmarketing study commitments are progressing toward completion for the period of our review.

We recognize that our recommendation that FDA instruct drug applicants to provide additional, meaningful information in their ASRs could require regulatory changes. In response, we added language to our recommendation acknowledging that FDA may need to seek regulatory changes to improve its system for monitoring postmarketing study commitments.

We also made other minor changes to our report based on FDA's technical comments.

▶ E N D N O T E S

¹ Federal Food, Drug, and Cosmetic Act of 1938, as amended. 21 U.S.C. § 355.

² Drug applicants typically are pharmaceutical or biotechnology companies seeking FDA's approval to market a new drug by submitting a new drug application.

³ Department of Health & Human Services, Food and Drug Administration, "Report to Congress on Postmarketing Studies [FDAMA 130]," April 2002.

⁴ Department of Health & Human Services, Office of Inspector General, "Postmarketing Studies of Prescription Drugs" (OEI-03-94-00760), May 1996.

⁵ Department of Health & Human Services, Food and Drug Administration, "Report to Congress on Postmarketing Studies [FDAMA 130]," April 2002.

⁶ Department of Health & Human Services, Food and Drug Administration, "Report to Congress on Postmarketing Studies [FDAMA 130]," April 2002, p. 1.

⁷ See, for example: Henderson, D. June 1, 2005. "Speedy drug-review process 'broken.'" Boston Globe: D3.

Also see: Fontanarosa, P.B., Rennie, D., and DeAngelis, C.D. December 1, 2004. "Postmarketing Surveillance—Lack of vigilance, lack of trust." *Journal of the American Medical Association* 292 (21): 2647-2650.

⁸ The following are the four situations in which FDA can require drug applicants to conduct postmarketing studies:

Accelerated approval. FDA may approve a drug based on a surrogate clinical endpoint. For example, FDA may approve a cancer drug based on the surrogate endpoint that the drug reduces tumor size, instead of the endpoint of increased life expectancy. In such cases, FDA requires

the applicant to conduct postmarketing studies to verify the safety and efficacy of the drug after it is on the market. FDA may withdraw the drug if the studies do not demonstrate effectiveness, raise safety concerns, or are not completed with due diligence. See 21 U.S.C. 356, 21 CFR § 314.510, and 21 CFR § 314.530.

Deferred pediatric studies. FDA requires all new drugs that are likely to be used in pediatric patients to demonstrate, prior to approval, their safety and efficacy in relevant pediatric populations. However, FDA may defer this requirement until after the drug is approved for use in adults. When FDA grants a deferral, it requires the applicant to conduct postmarketing studies to demonstrate the safety and efficacy of the drug in pediatric participants. If the applicant fails to conduct such studies, FDA may consider the drug misbranded and may authorize an injunction, seizure, or other action. See: Pediatric Research Equity Act of 2003; 21 CFR § 314.55; 21 U.S.C. §§ 331-334; and 63 Federal Register 66,631, December 2, 1998, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients.

Animal efficacy rule. FDA may approve a drug based solely on animal studies when clinical studies in humans cannot be conducted ethically. Under these circumstances, FDA requires the applicant to conduct postmarketing studies to verify and assess the safety and efficacy of the drug in humans. If the applicant fails to perform the studies with due diligence, FDA may withdraw the drug. See 21 CFR § 314.610 and 21 CFR § 314.620.

Determination to revoke approval. FDA may require an applicant to conduct a postmarketing study after the drug is already approved if information is needed to determine whether the approval of the drug should be revoked. This is typically used for cases in which there is a serious concern about safety. (FDA does not track these situations in its database of postmarketing study commitments.) See 21 U.S.C. §§ 355(e) and 355(k).

⁹ 21 U.S.C. § 356b.

¹⁰ Department of Health & Human Services, Food and Drug Administration, “Report to Congress on Postmarketing Studies [FDAMA 130],” April 2002.

¹¹ 21 U.S.C. § 356b.

¹² Prior to FDAMA, drug applicants were required to report on postmarketing studies. 21 CFR § 314.81. However, Section 130(a) of Title I of FDAMA (1) requires applicants to provide more detailed information on the status of their commitments and (2) made certain information publicly available.

¹³ 65 Federal Register 64,607, October 30, 2000, Postmarketing Studies for Approved Human Drug and Licensed Biological Products: Status Reports.

¹⁴ 21 CFR § 314.81(b)(2)(vii).

¹⁵ Although these studies are excluded from FDAMA, they still must be reported to FDA under a different reporting requirement, 21 CFR § 314.81(b)(2)(viii).

¹⁶ 21 CFR § 314.81(b)(2)(vii).

¹⁷ 21 CFR § 314.81(b)(2).

¹⁸ Department of Health & Human Services, Food and Drug Administration, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” February 2006, p. 14.

¹⁹ Department of Health & Human Services, Food and Drug Administration, Draft Guidance, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” April 2001.

²⁰ Department of Health & Human Services, Food and Drug Administration, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” February 2006.

²¹ 21 U.S.C. § 356b(d).

²² Department of Health & Human Services, Food and Drug Administration, Press Release, “FDA Acts to Strengthen the Safety Program for Marketed Drugs,” November 5, 2004.

²³ Department of Health & Human Services, Press Release, “Reforms Will Improve Oversight and Openness at FDA,” February 15, 2005.

²⁴ Food and Drug Administration, Center for Drug Evaluation and Research, Manual of Policies and Procedures, “Procedures for Tracking and Reviewing Phase 4 Commitments,” effective date October 1, 1996.

²⁵ Postmarketing study commitment database available online at <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>. Last accessed May 19, 2006.

²⁶ Food and Drug Administration, Center for Drug Evaluation and Research, Manual of Policies and Procedures, “Procedures for Completing and Processing the Form ‘Annual Report Review: Postmarketing Study Commitment Summary,’” effective date March 16, 2005.

²⁷ Food and Drug Administration, Center for Drug Evaluation and Research, Manual of Policies and Procedures, “Procedures for Tracking and Reviewing Phase 4 Commitments,” effective date October 1, 1996.

²⁸ Department of Health & Human Services, Office of Inspector General, “Postmarketing Studies of Prescription Drugs” (OEI-03-94-00760), May 1996.

²⁹ Department of Health & Human Services, Office of Inspector General, “FDA’s Review Process for New Drug Applications” (OEI-01-01-00590), March 2003.

³⁰ On October 1, 2003, FDA transferred certain product oversight responsibilities from the Center for Biologics Evaluation and Research (CBER) to CDER. CBER postmarketing commitments and its review divisions were excluded from this review.

³¹ 21 CFR § 314.81(b)(2)(vii)(a)(8).

³² Department of Health & Human Services, Food and Drug Administration, Draft Guidance, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” April 2001.

³³ Department of Health & Human Services, Food and Drug Administration, Draft Guidance, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” April 2001, p. 14.

The finalized guidance is consistent with the draft guidance. See Department of Health & Human Services, Food and Drug Administration, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” February 2006, p. 12.

³⁴ Department of Health & Human Services, Food and Drug Administration, Draft Guidance, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” April 2001, p. 15.

The finalized guidance is consistent with the draft guidance. See Department of Health & Human Services, Food and Drug Administration, “Guidance for Industry, Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997,” February 2006, p. 14.

³⁵ We reviewed ASRs submitted in fiscal year 2004 and compared the commitments addressed in the reports to the commitments listed in the database of postmarketing study commitments. We identified examples of new drug applications and postmarketing commitments that were listed in the database and, therefore, would have required ASRs; yet ASRs were missing for some of these new drug applications. (We cross-referenced the database to a list, provided to us by CDER, of all annual reports that should have included an update on postmarketing study commitments in fiscal year 2004.) We requested that CDER look into some of the missing ASRs.

³⁶ 21 CFR § 314.81(b)(2)(vii).

³⁷ CDER provided us with a list of 160 commitments associated with 68 unique new drug applications that were fulfilled in fiscal year 2004; we were able to analyze 145 of these commitments associated with 59 unique new drug applications. The others were excluded because they were outside the period of our inquiry and/or could not be matched to commitments in CDER's database of postmarketing study commitments.

³⁸ When the original projected completion date and/or the final report submission date were not available, we could not determine the amount of time it took for postmarketing study commitments to be fulfilled.

³⁹ 65 Federal Register 64,607, 64,608, October 30, 2000, Postmarketing Studies for Approved Human Drug and Licensed Biological Products; Status Reports.

⁴⁰ Food and Drug Administration, Center for Drug Evaluation and Research, Manual of Policies and Procedures, "Procedures for Completing and Processing the Form 'Annual Report Review: Postmarketing Study Commitment Summary,'" effective date March 16, 2005.

METHODOLOGY

Analysis of FDA's Postmarketing Database

We obtained from the Food and Drug Administration (FDA) its data on the status of all postmarketing study commitments associated with new drug applications issued between October 1, 1989, and September 30, 2004. To obtain additional data on these commitments, we requested that FDA link the database of postmarketing study commitments to its Oracle-based management information system, which contains information including drugs' approval dates, drugs' review divisions, whether drugs are new molecular entities (NMEs), and types of commitments.

Our analysis of postmarketing study commitments is based on a population of 2,353 commitments. The database actually contained 2,381 unique postmarketing study commitments, but we excluded 28 because they were associated with new drug applications approved before October 1, 1989, and therefore, outside the scope of our review. We did include in our analysis 279 studies that are associated with more than one new drug application.

One limitation of the database is that it does not generally contain the dates on which commitments were initiated (most, but not all, commitments are made at the time of drug approval). Therefore, to associate commitments with fiscal years, we linked each commitment to the approval date of its associated new drug application.

The database has additional limits. First, it does not contain many dates that would be useful in monitoring postmarketing study commitments. Further, prior to the implementation of the Food and Drug Administration Modernization Act of 1997 (FDAMA), postmarketing study commitments were not required to have schedules. Therefore, one cannot determine whether postmarketing study commitments associated with new drug applications from 2001 or earlier are, or were, on schedule.

We used Microsoft Excel® to perform various trend analyses. We conducted trend analyses of postmarketing study commitments associated with new drug applications by fiscal year, study type, study category, review division, and study status. We conducted the same trend analyses for postmarketing study commitments associated with NMEs, which are a subset of new drug applications.

Review of ASRs and Corresponding FDA Reviews

We obtained from FDA a list of the 336 annual reports that were or should have been received from drug applicants in fiscal year 2004 and that should have contained annual status reports (ASRs) for open postmarketing study commitments. We classified these submissions based on whether they contained required information. We reviewed all commitments listed in the 217 ASRs in which drug applicants actually provided information on their open postmarketing study commitments. Because we determined that the numbering of commitments in ASRs was not always consistent with the numbering of commitments in the database of postmarketing study commitments, we attempted to match each commitment listed in an ASR to a commitment in the database by using the descriptions of the commitments. We found 788 commitments for which there were matches, and excluded all remaining commitments from our analysis. We used a set protocol to extract information from the reports into a Microsoft Access® database.

We also reviewed all available FDA validations and other supporting documentation associated with postmarketing study commitments for fiscal year 2004 ASRs. FDA provided us with 66 validation forms, of which we excluded 1 because it addressed only control, manufacturing, and chemistry studies; these were outside the scope of our review. We reviewed this documentation to determine (1) the extent to which the reviews were completed on time and (2) the extent to which FDA reviewers concurred with progress on commitments as reported by drug applicants. We used a set protocol to extract information from these documents into a Microsoft Access® database.

Review of FDA Fulfillment Letters

To determine how long it takes to complete postmarketing study commitments, we reviewed all FDA fulfillment letters issued in fiscal year 2004. FDA sends fulfillment letters to drug applicants to acknowledge completed commitments. We had to review fulfillment letters because the dates associated with postmarketing study commitments, including fulfillment dates, were not required in ASRs before the implementation of FDAMA and, therefore, were not consistently tracked in FDA's database of postmarketing study commitments.

FDA provided us with fulfillment letters for 160 postmarketing commitments that were associated with 68 unique new drug applications. We excluded 15 commitments because they were either

not listed in the database or there was a discrepancy between the details in the fulfillment letters and the descriptions in the database that led us to question whether there was actually a match. Of the remaining 145 commitments, we had to exclude 127 for which we could not determine the original scheduled completion dates and/or the dates on which final reports were submitted; this left us with 18 commitments to analyze.

Case Studies

Based on our analysis of the fiscal year 2004 fulfillment letters for postmarketing study commitments, we identified the nine commitments that were fulfilled the latest. We obtained all ASRs and corresponding FDA reviews associated with these commitments from the time the commitments were made through fulfillment, as well as any additional correspondence regarding those commitments. We reviewed this documentation to determine: (1) why commitments were late and (2) the extent to which FDA reviewers concurred with the progress of commitments as reported by drug applicants. We also attempted to determine the extent to which FDA reviewers followed up with drug applicants regarding any issues the reviewers may have had with the commitments.

Interviews With FDA Officials

We interviewed project managers at 14 of the 16 review divisions within FDA. We did not interview officials at the two divisions responsible for overseeing therapeutic biologic drugs because these drugs were outside the scope of our inspection.

We used a structured questionnaire to conduct the interviews. The questionnaire addressed: (1) FDA's policies and procedures for monitoring postmarketing study commitments, (2) the challenges FDA faces in monitoring postmarketing study commitments, and (3) recommendations for improving the process of monitoring postmarketing study commitments. We conducted all interviews by telephone.

Review of FDA Policies, Procedures, and Guidance Documents

We obtained and reviewed all relevant policies, procedures, and guidance documents for postmarketing study commitments issued by FDA. We used these documents to better understand the process for monitoring postmarketing study commitments.

DATA TABLES

Appendix Table 1. New Drug Applications With Postmarketing Study Commitments, by Fiscal Year, 1990–2004			
Year of Drug Approval	Number of New Drug Applications	Number of New Drug Applications With at Least One Postmarketing Study Commitment	Percentage of New Drug Applications With at Least One Postmarketing Study Commitment
1990	70	18	26
1991	62	26	42
1992	86	38	44
1993	84	23	27
1994	63	37	59
1995	71	32	45
1996	120	65	54
1997	124	61	49
1998	107	47	44
1999	77	39	51
2000	106	60	57
2001	71	36	51
2002	64	34	53
2003	86	40	47
2004	93	66	71
Overall	1,284	622	48

Source: Office of Inspector General analysis of FDA data, 2005.

Appendix Table 2. Postmarketing Study Commitments by Review Division From Fiscal Years 1990–2004		
CDER Review Division	Number of Postmarketing Study Commitments	Percentage of Postmarketing Study Commitments
Anti-Viral Drug Products	601	26
Special Pathogen and Immunologic Drug Products	335	14
Oncology Drug Products	197	8
Neuropharmacological Drug Products	189	8
Metabolic and Endocrine Drug Products	153	7
Anesthetic, Critical Care, and Addiction Drug Products	129	5
Gastro-Intestinal and Coagulation Drug Products	117	5
Dermatologic and Dental Drug Products	115	5
Medical Imaging and Radiopharmaceutical Drug Products	102	4
Anti-Infective Drug Products	101	4
Reproductive and Urologic Drug Products	91	4
Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products	77	3
Over-the-Counter Drug Products	68	3
Cardio-Renal Drug Products	38	2
Pulmonary and Allergy Drug Products	40	2
Total	2,353	100

Note: This table attributes postmarketing study commitments to the CDER review divisions that existed between 1990 and 2004.

Source: Office of Inspector General analysis of FDA data, 2005.

Appendix Table 3. Required Elements Missing From Fiscal Year 2004 ASRs, per Postmarketing Study Commitment

Element	Number of Postmarketing Study Commitments for Which Element Was Missing	Percentage of Postmarketing Study Commitments for Which Element Was Missing*
Date of U.S. Approval	149	19
Date of Study Commitment	145	18
Schedule	141	18
Explanation of Status	78	10
Applicant Name	75	10
Status of Commitment	65	8
Description of Commitment	18	2
Application Number	10	1
Product Name	6	< 1

* Column does not sum to 100 because rows are independent of one another.

Source: Office of Inspector General analysis of FDA data, 2005.


Appendix Table 4. Length of Time It Took FDA to Validate Fiscal Year 2004 ASRs

Length of Time Between Submission and Validation	Number of Validations	Percentage of Validations
Less Than 90 Days	29	45
Between 91 and 180 Days	19	29
More Than 180 Days	17	26
Total	65	100

Source: Office of Inspector General analysis of FDA data, 2005.

▶ A P P E N D I X C

Agency Comments

 DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 16 2006

DATE:


TO: Inspector General

FROM: Acting Commissioner of Food and Drugs

SUBJECT: FDA's Comments on OIG Draft Report: "FDA's Monitoring of Postmarketing Study Commitments," OEI-01-04-00390

Thank you for the opportunity to review and comment on the Draft Report: "FDA's Monitoring of Postmarketing Study Commitments," OEI-01-04-00390. The Food and Drug Administration's comments and status updates are in the attachment.

If you need additional information, please contact Regina Ledesma at (301) 827-1223.


Andrew C. von Eschenbach, M.D.

Attachment

FDA Comments on OIG Draft Report
 "FDA's Monitoring of Postmarketing Study Commitments," (OEI-01-04-00390)

The Food and Drug Administration is pleased to provide comments on the OIG Draft Report. While we embrace several recommendations for improvement that are outlined in the report, we do not agree that FDA cannot readily identify whether or how timely postmarketing study commitments (PMCs) are progressing toward completion. Working under statutory and regulatory authorities and in the face of competing regulatory responsibilities, FDA takes its obligations under Food and Drug Administration Modernization Act for monitoring the progress of PMCs and making certain information publicly available very seriously. This is evidenced by FDA's ongoing efforts aimed at: (1) enhancing the PMC database and reporting functionalities; (2) completing specialized training for the review divisions on the overall management of PMCs with a focus on the procedure for validating annual status reports (MaPP 6004.2); and (3) hiring of an outside contractor to conduct a thorough analysis of the PMC process to gain greater internal consistency in how FDA requires, requests, facilitates and reviews PMCs.

The following are FDA's comments on the broad recommendations made in the report:

1. Instruct drug applicants to provide additional, meaningful information in their ASRs.

Comment: The Agency does not concur. The current regulations for PMC annual status reports have specific content and format elements for industry to follow. A provision for additional information would require that new regulations be written.

2. Improve the management information system for monitoring postmarketing study commitments so that it provides timely, accurate, and useful information.

Comment: The Agency concurs. FDA continually assesses its information systems to determine what improvements can be made. The database is currently being redesigned to provide enhanced data entry and retrieval capabilities.

- o Ensure that commitments are numbered uniquely and logically.

Comment: The Agency concurs. The CDER letter templates have been modified since the revised reporting regulations went into effect in 2001. These templates provide staff with clear instructions on how to number the PMCs and delineate required PMCs from those that are agreed-upon. The PMCs are entered under the application number and then 1-N. The numbering was an issue primarily with the older commitments not always exactly matching up with how the PMCs are numbered in the approval letter or how industry reported them in their annual status reports. The implementation of the new letter templates were enhanced to improve the

consistency of how PMCs are numbered in letters. In the ongoing PMC training for the divisions emphasis is made to make sure all PMC are numbered according to the instructions.

- o Ensure that the database is populated with useful information.

Comment: FDA concurs with this recommendation, while noting that many of the PMCs reviewed by OIG were older commitments that pre-dated FDAMA and the 2001 reporting regulations. Therefore, they may not have had study schedules established at the time of approval. Additionally, it should be noted that the database is populated after verification of the information contained in annual status reports, and deficient or missing reports impact FDA's ability to effectively populate the database.

- o Develop a reporting capability that readily identifies late ASRs and outstanding commitments.

Comment: While FDA acknowledges the need for enhanced reports and concurs, this internal report-generating capability already exists. FDA's current database can generate a variety of PMC reports, including a report listing annual status reports received for applications with outstanding commitments. This report also includes in its output a listing of the outstanding PMCs for that application and the current status. Future planned improvements include an expanded and enhanced cache of reports as part of the Document Archiving, Reporting and Regulatory Tracking System (DARRTS), CDER's new single, integrated system that will eventually house many of the Center's core tracking systems.

3. Ensure that postmarketing study commitments are being monitored and that ASRs are being validated.

Comment: The Agency concurs. CDER implemented the procedure for validating PMC annual status reports (MaPP 6004.2) in March 2005; and, at the time of OIG's inspection, these formal procedures were only newly instituted. Since that time, the validation of annual status reports is more routinely accomplished within CDER's many resource-intensive and competing regulatory responsibilities.

We appreciated your informative report. If you need additional information, please have your staff contact Regina Ledesma at (301) 827-1223.



A C K N O W L E D G M E N T S

This report was prepared under the direction of Joyce M. Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Russell W. Hereford, Deputy Regional Inspector General. Other principal Office of Evaluation and Inspections staff who contributed include:

Aimée Golbitz, *Team Leader*

Christopher Galvin, *Program Analyst*

Michael Flood, *Program Analyst*

Ayana Everett, *Program Specialist*

Linda Hall Moody, *Program Specialist*

Genevieve Nowolinski, *Program Specialist*

Elise Stein, *Director, Public Health and Human Services*