

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**POSTMARKETING STUDIES OF
PRESCRIPTION DRUGS**



JUNE GIBBS BROWN
Inspector General

MAY 1996
OEI-03-94-00760

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EXECUTIVE SUMMARY

PURPOSE

Our report describes the effectiveness of the Food and Drug Administration's (FDA) monitoring of postmarketing studies for prescription drugs.

BACKGROUND

Postmarketing studies--investigational drug studies conducted after FDA marketing approval--can have an impact on how drugs are prescribed and used. A company's agreement to conduct an FDA-requested postmarketing study is called a postmarketing or phase iv commitment.

Responsibility for monitoring phase iv commitments lies with the Offices of Drug Evaluation in the Center for Drug Evaluation and Research (CDER). A division in the CDER's Office of Management was assigned the responsibility of identifying commitments for all new drugs and tracking their status. The tracking results are published for CDER's internal use as the *Phase IV Postapproval Research List*.

Our report provides FDA management with an overview of monitoring procedures and outcomes, focusing on new molecular entities.

FINDINGS

The number of new drugs with postmarketing commitments is increasing. In the 1970s, the highest annual percentage of such drugs was 33 percent compared to a high of 70 percent in the 1990s.

There are no formal standards and procedures for monitoring or for establishing whether a postmarketing commitment is met.

While the Phase IV Postapproval Research List contains important and useful information, it is not a fully effective management tool in its current form. Its format precludes summarization of records, it is not updated regularly, and significant data elements are not captured consistently.

The FDA is taking some steps to improve the tracking of phase iv commitments.

RECOMMENDATIONS

We recognize there are limited resources and FDA's priority is the review of premarketing studies. This is especially true with the shorter time frames in which FDA reviews premarketing studies under the Prescription Drug User Fee Act of 1992.

We also recognize FDA is interested in improving data management for postmarketing commitments and is taking steps in that direction.

As our report indicates, FDA is requesting postmarketing studies for an increasing number of drugs. We believe it is reasonable to expect FDA to determine whether or not submitted studies fulfill the commitments. Until commitments are more systematically monitored and brought to closure, FDA is not availing itself of a management tool with which to assess the appropriateness of its requests and plan for the future.

We recommend that FDA:

- ▶ *establish standards, procedures, or guidelines for carrying out monitoring and tracking objectives; and*
- ▶ *establish accountability for monitoring, tracking, and bringing commitments to closure.*

Below are some ideas for FDA to consider in order to streamline data management:

- Assign authority to specific personnel for carrying out management's objectives. Establish a coordinator with authority to (1) represent all offices involved in monitoring, tracking, and bringing commitments to closure; and (2) ensure that there is a quality control system for the commitments database.
- Reduce the number of documents that have to be researched in order to identify the status of commitments; and use standard notations on these documents to signify how each document affects the status of the commitment.
- Establish descriptive categories for (1) types of studies requested and (2) status of commitments.
- Put the database of postmarketing commitments on-line in the review divisions and allow authorized individuals to update records as soon as an action occurs or a determination is made.

FDA COMMENTS

The FDA agrees with this report's findings and recommendations. A draft directive that establishes procedures and provides guidance is undergoing review within CDER is expected to be finalized by the end of June 1996. (Appendix C contains FDA's comments in full.)

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INTRODUCTION

PURPOSE

This report describes the effectiveness of the Food and Drug Administration's (FDA) monitoring of postmarketing studies for prescription drugs.

BACKGROUND

Definition of Postmarketing Studies

Before drug companies can market new drugs in the United States, they must apply to FDA and receive approval. Normally, drug manufacturers test new drugs in three phases of studies prior to applying for marketing approval. The premarketing studies determine the drug's safety and efficacy under controlled conditions.

Prior to or after granting marketing approval, FDA may ask the manufacturer to conduct a "phase iv" or "postmarketing" study--synonymous terms in this report. This request is made if FDA concludes that additional information, while not essential for approval, will improve the prescribing and use of the drug. Postmarketing studies may confirm existing data, raise questions, or provide new data. Drug companies may initiate postmarketing studies without an FDA request, but in this report we are only addressing studies requested by FDA.

As of the early 1990s, new regulations at 21 CFR 314.500, make it possible for FDA to grant marketing approval under an accelerated review process for a small number of drugs that treat serious and life-threatening illnesses.¹ When FDA uses the accelerated review process, the drug is available sooner but with less immediate clinical and safety information than the normal review process requires. When using the accelerated process, FDA can require postmarketing studies and can withdraw marketing approval if the studies are not completed with due diligence.

For most new drugs, FDA does not have the same kind of legal authority to require completion of postmarketing studies. Nevertheless, there is a tradition of FDA requesting studies and companies agreeing to conduct them. A company's agreement to conduct a study is called a phase iv or postmarketing commitment. In this report we use the term commitment when discussing agreed-upon phase iv studies for drugs approved under the normal and accelerated processes.

Who Does the Monitoring

Monitoring includes following-up on a phase iv commitment, reviewing any data the company submits, and tracking the status of the commitment until closure is reached.²

Primary responsibility for monitoring commitments lies with the reviewers handling a drug company's application for marketing approval. The reviewers are located in divisions of the Offices of Drug Evaluation in FDA's Center for Drug Evaluation and Research. (Hereinafter the name of the Center is abbreviated as the Center for Drugs). In the course of analyzing a drug company's application, a reviewer may request that the company conduct one or more postmarketing studies. If the drug under review is a not a new molecular entity,³ the request is cleared by the review division director. Requests relative to a new molecular entity are cleared at the level of office director. The company also enters into discussions about the request before making a commitment to conduct any studies.

The FDA usually enumerates a company's postmarketing commitments in a letter to the company. Then, as the company submits data relative to its commitments, reviewers (ideally the same ones that requested the phase iv study) determine if any action is necessary. The kind of action depends on the submission and might include a labeling change.

While reviewers keep track of the phase iv commitments for drugs they reviewed, a division in the Office of Management, Center for Drugs, was given the responsibility for tracking the status of commitments for all drugs approved in the Center. This is the Division of Drug Information Resources (DDIR). Periodically, DDIR staff research documents in the review divisions to identify commitments and their status. Data extracted from the documents are organized in a word-processing file, and the file is published for the Center's internal use under the title, *Phase IV Postapproval Research List* (hereinafter abbreviated as *Phase IV List*).

What the *Phase IV List* Contains

The *Phase IV List* contains a record for each drug (both prescription and over-the-counter) that has postmarketing commitments. Records are only of commitments made on original drug applications. There is no Centerwide tracking of commitments for supplementary applications or for postmarketing studies that were not requested by FDA.

Each drug record briefly describes the commitments and their status as of the last data collection period, and cites the documentary sources of that information. Sources used to identify the commitments are generally one of two types of form letters review divisions send to drug companies, but other documents are also used. The status is derived from drug company correspondence, supplements, progress reports, periodic reports, annual reports, and from FDA correspondence, reviewer reports, meeting minutes, and telephone or electronic contact reports.

There may be any number of commitments per drug, and they are listed together in the drug's record. When all the commitments for a particular drug are met, the record for that drug moves from the *Phase IV List's* Pending Commitments List to its Commitments Met or Released List.

In 1988, DDIR conducted the first and only internal analysis of information in the *Phase IV List*. The result was a description of drugs with postmarketing commitments between 1972 and 1988, types of studies agreed to, and drug company compliance.⁴

SCOPE AND METHODOLOGY

We conducted our data collection and analysis between February and October of 1995. All data is from FDA's Center for Drugs in Rockville, MD.

We focused on all new molecular entities (NMEs) approved from January 1, 1987 to December 31, 1993, including NMEs approved under the accelerated review process. We limited our analysis to NMEs to focus on drugs most likely to have postmarketing commitments. New molecular entities are usually under 30 percent of all new drug approvals, and they are prescription drugs which have never been marketed as a single entity or as part of a combination product. We selected 1993 as the cutoff year for drug approval because it left 2 years--from 1993 to 1995--to show if companies took action on their commitments.

We used the most recent version (1993) of the *Phase IV List* to determine which of the NMEs had phase iv commitments. Our identifications were verified by DDIR.

Since DDIR was planning to update the *Phase IV List* in 1995, it agreed to update the status of the commitments in our study's universe and send them to us in advance of its completing the update for all its records. As a result, we were able to analyze the status of commitments as of August 1995. The status categories we created for the analysis are similar to those used by DDIR in 1988 but are somewhat more explanatory. Both sets of status categories are in Appendix A.

We (1) quantified the number and type of postmarketing studies for NMEs; (2) identified the pharmacologic-therapeutic classification of the NMEs; (3) categorized each phase iv study according to its current status; and (4) when possible, determined the length of time between a company's submission of a study and FDA's determination of closure. The tables and figure in this report are the result of our analysis of data in FDA's *Phase IV List* and Management Information System.

In addition to the above, we conducted 45 on-site interviews with FDA's professional, scientific, and technical staff in the areas of drug review, drug information resources, document management, and computer design. The respondents included office directors, division directors, drug reviewers, project management staff (also known as consumer safety officers), drug information officers, and technical information specialists. Ninety-three percent of the respondents were in the review divisions and DDIR. Each of those respondents received the interview questions in advance.

When we began our study there were 10 review divisions, each specializing in certain drugs.⁵ We conducted interviews in 6 of the 10 review divisions, including the two

that have used the accelerated approval process. The Center for Drugs has since undergone a reorganization, and the number of review divisions has changed.

Under separate cover, we gave the Center for Drugs our data analysis that serves as an extension of DDIR's 1988 analysis but which is not directly related to findings herein.

Our study was conducted in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

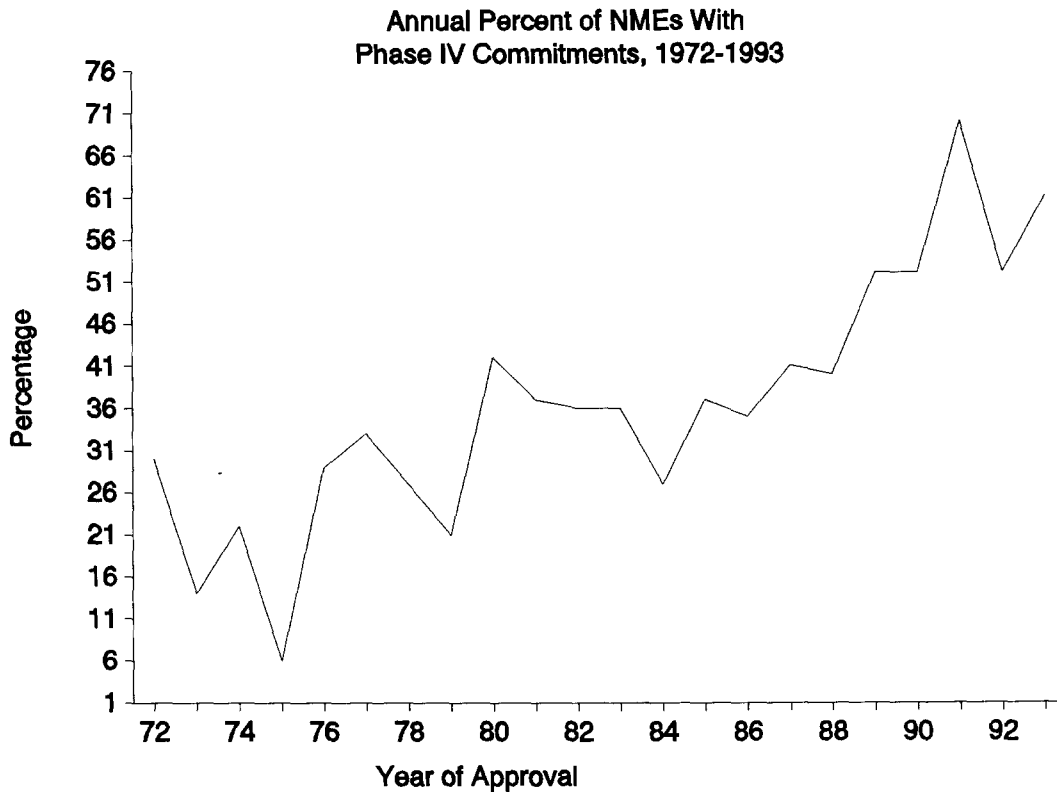
FINDINGS

THE NUMBER OF NEW DRUGS WITH POSTMARKETING COMMITMENTS IS INCREASING.

Percentage of Drugs with Postmarketing Commitments

While the annual percentage of new molecular entities (NMEs) with commitments varies, there has been an upward trend as shown in Figure A. In the 1970s, the highest percentage of such drugs was 33 percent compared to a high of 70 percent in the 1990s.

Figure A



More than half of the NMEs in our study period, 1987-1993, have postmarketing commitments. For these years, FDA approved a total of 169 NMEs including 2 under the accelerated approval process. Fifty-three percent, or 90 of the 169 drugs had commitments. Table 1 on the next page shows the percent by year.

There was a total of 385 commitments for the 90 drugs, and an average of 4 commitments per drug as shown in Table 2. Twenty-five of the 90 drugs had only one

commitment each. Of the 385 commitments, 35 were for the 2 NMEs approved under the accelerated process.

Table 1

PHASE IV NMEs* AS A PERCENTAGE OF TOTAL NMEs 1987-1993		
Year	Total NMEs	Phase IV NMEs
1987	21	9 (43%)
1988	20	6 (30%)
1989	24	12 (50%)
1990	23	12 (52%)
1991	30	21 (70%)
1992	25	13 (52%)
1993	26	17 (65%)
TOTAL	169	90 (53%)

*NMEs with phase iv (postmarketing) commitments

Table 2

AVERAGE NUMBER OF PHASE IV COMMITMENTS PER PHASE IV NME* 1987-1993			
Year of Drug Approval	Number of Phase IV NMEs	Number of Phase IV Commitments	Average Number of Commitments Per NME
1987	9	37	4
1988	6	19	3
1989	12	36	3
1990	12	44	4
1991	21	96	5
1992	13	80	6
1993	17	73	4
TOTAL	90	385	4

*NMEs with phase iv (postmarketing) commitments

Status of Postmarketing Commitments

The FDA data indicates that out of the 385 phase iv studies it asked companies to conduct, 150 are currently in progress and 146 were completed and submitted to FDA.

In other words, 296 studies, or 77 percent of the studies, are either in progress or have been submitted. The table in Appendix B shows the status of commitments as of August 1995 for all NMEs approved between 1987 and 1993, including NMEs approved under the accelerated review process.

Fifty-seven percent or 88 of the 150 studies in progress are actually underway. The remaining 62 studies break out as follows. One study is perpetual (i.e., an ongoing surveillance study); 11 were halted; and 50 were completed but a report has not yet been submitted to FDA.

Of the 146 studies that were submitted to FDA, FDA reviewed 40 and found 39 acceptable and only 1 not acceptable. It appears to have taken FDA an average of 16 months to determine that 25 studies were acceptable. Dates that would have allowed us to calculate an average time for all 39 studies are missing from the *Phase IV List*. Nine of the 39 studies FDA found acceptable were studies for accelerated NMEs. Five of these nine studies had determinations within 11 days to 21 months after the date of the study's submission.⁶

The FDA data does not indicate whether 106 out of the 146 submitted studies are acceptable or not. Dates in the *Phase IV List* indicate that 30 of the 106 studies have been without a determination for 2 to 7-1/2 years. Dates for the remaining 76 studies are missing. One study for an accelerated NME has not had a determination for almost 3 years.⁷

Thirty-five studies out of the total 385 have not yet begun, either because the company (a) is postponing action until FDA reviews a supplement application, (b) did not agree to conduct the study, or (c) plans to start the study in the future.

The FDA released companies from 23 of the 385 commitments. Twelve of these released commitments were for drugs that are not marketed. For the remaining 11 studies in this status category, either (a) the studies were not feasible, (b) FDA's questions were answered by other studies, or (c) the reason for release was not clearly explained in the *Phase IV List*.

There was no status information at FDA for 31 (eight percent) of the 385 studies. All 31 studies were for drugs approved from 1990 through 1993.

THERE ARE NO FORMAL STANDARDS AND PROCEDURES FOR MONITORING OR ESTABLISHING WHETHER A COMMITMENT IS MET.

Review Divisions

There are no formal Centerwide standards and procedures for monitoring postmarketing studies. Monitoring in the review divisions is up to individuals. Reviewers request postmarketing studies and review company submissions in their normal scope of work which is reviewing investigational new drug applications, new

drug applications, and efficacy and labeling supplements. However, following-up on a commitment and reviewing a phase iv submission are done as time allows and are dependent on the commitment's relative importance.

There is no formal mechanism for establishing whether a commitment is met and then taking the commitment out of the pending section of the *Phase IV List*. There are indications that in some cases someone has determined that phase iv studies were acceptable and the commitments were met. For example, we found such determinations for 39 of the 146 submitted studies. During our interviews, most review division respondents said the reviewer would, at least initially, decide whether a commitment was met. However, no one has the formal responsibility of determining and recording whether or not a company's phase iv submission meets the commitment. This may explain why data in the *Phase IV List* indicates that 106 submitted studies for NMEs approved from 1987 through 1993 are still without determinations.

The review divisions have a procedure for advising drug companies of their commitments around the time the new drug receives market approval. But, they do not have a procedure for notifying a company when and whether their phase iv submissions have been reviewed and accepted as fulfillment of the commitments. While individual reviewers may relay this to drug companies, the records do not indicate that such notification occurs.

Under the current monitoring which relies on individuals, reviewers may or may not have ways of reminding themselves to contact a company about a commitment. Reviewers either rely on reminders from project management staff, have their own tickler system, or respond when a question arises. But reviewers and review division directors alike believe the important studies are memorable and most companies meet their commitments. Some respondents said relying on individuals within an informal system could be a problem. They cited that a reviewer could leave the division and remaining staff would not be aware of pending commitments.

While some review division respondents believe there should be guidelines regarding phase iv monitoring, a greater number feel the current way things are done is good enough given limited resources. Most of these respondents feel it is unnecessary to have formal procedures because in most cases it is extremely difficult for FDA to enforce compliance. They feel once the drug is approved, it is up to the company to take the next step regarding their commitment.

Phase IV List

While the *Phase IV List* is a tool the review divisions could use as a reminder of which commitments are pending, most reviewers and division directors were not aware of its existence. The office directors and project management staff knew of the *Phase IV List* but they did not make full use of it.

The informality of phase iv tracking in the review divisions hampers DDIR in its ability to collect complete and timely phase iv data for the Centerwide *Phase IV List*. All sources of postmarketing data are located in review division documents. But because documents containing phase iv information are so numerous and are not indexed, identifying them is very time-consuming. In addition, there is no way for the tracking staff to be sure they have located all the relevant documents. It is only when documents indicate that a phase iv study fulfilled the commitment for a particular drug that DDIR removes it from the pending section of the *Phase IV List*.

Currently, there is no formal mechanism by which DDIR can receive feedback from the review divisions about the *Phase IV List*. Respondents in DDIR say updating the *Phase IV List* requires a great deal of work and they hope their product is useful. But without feedback from end-users they do not know if the *Phase IV List* is addressing user needs.

WHILE THE *Phase IV List* CONTAINS IMPORTANT INFORMATION, IT IS NOT A FULLY EFFECTIVE MANAGEMENT TOOL IN ITS CURRENT FORM.

Important Information

The *Phase IV List* is the only instrument containing postmarketing commitment data on every drug (including NMEs) approved by the Center for Drugs. The *Phase IV List* is made up of one record for each drug with commitments, and the records are grouped according to the review division handling the drug. A record contains identifiers for the drug, the drug's approval date, a narrative description of the commitments, a narrative description of the status, the name and date of the sources of information, and the name of a contact person in the review division. We were able to use the *Phase IV List* for most of our analyses.

Timeliness and Completeness

The *Phase IV List* is not updated on a regular or frequent basis, and certain data elements are not captured consistently. At the time of our interviews in mid-1995, the *Phase IV List* was already 2 years old. Many of the dates that would give management time frames for company or FDA activity were missing. Also, drugs approved under the accelerated review process were not identified as such. However, the timeliness and completeness of data is affected by the lack of standards and procedures for monitoring phase iv studies in the review divisions. Without procedures to keep abreast of commitments and to record that activity in a standard way, the same phase iv data cannot be captured consistently Centerwide.

Format

The *Phase IV List* does not contain summarizations of the numerous records. Two factors can explain the absence of summaries. One factor is that extended narratives are used in each record to describe a commitment and its status. The narrative

format makes it hard to see patterns or anomalies in the types of studies requested or in company compliance. While an individual can manually go through each record in the *Phase IV List*, create categories, and then count up items in the categories (as we did), this is very time-consuming. Furthermore, narratives are subject to interpretation and categorizing them for analysis is a matter of individual judgment.

The second factor is the type of computer software in which the information is stored. Currently, the information is in a word-processing program which cannot automatically summarize data. Given the nature of the data, the need for quick turn-around reporting, and the need for ease of data entry and changes, we believe more convenient software, such as a relational database, may be more appropriate.

THE FDA IS TAKING SOME STEPS TO IMPROVE THE TRACKING OF COMMITMENTS.

In late 1994, the Center for Drugs established a work group to look at tracking problems. As of September 1995 at least two improvements were being implemented. The first is that postmarketing commitments will be formally listed in a standard letter to the company. This will reduce the number of documents DDIR staff have to research in order to identify a new commitment. The second improvement is that the *Phase IV List* will be transferred from its current word-processing program to a database program.

The Center plans to continue its efforts to improve the tracking system. One goal is to have the *Phase IV List* on-line for greater accessibility. Another is to make company submissions more easily identifiable for tracking purposes.

RECOMMENDATIONS

We recognize that FDA has limited resources and its priority is the review of premarketing drug studies. This is especially true with the shorter time frames FDA has to review premarketing studies and new drug applications under the Prescription Drug User Fee Act of 1992 (P.L. 102-571). We also recognize that the Center for Drugs is interested in improving the data management system for postmarketing commitments and has started to do so. Since FDA work groups are currently meeting to improve tracking, this is an opportune time to make data collection less labor intensive and to create a system that meets the informational needs of senior management in the Center for Drugs.

As our report indicates, FDA is requesting postmarketing studies for an increasing number of new drugs, and most of the commitments are long-term in nature. Furthermore, for drugs approved under the accelerated review process, FDA can move to withdraw the drugs from the market if the postmarketing studies are not completed with due diligence.

Until the monitoring system is made less dependent on individual memory, FDA risks losing track of the commitments. Unless time frames are tracked and monitored, FDA cannot uniformly determine diligence on the part of drug companies. Until the commitments are monitored and tracked systematically, FDA is not availing itself of a management tool with which to assess the appropriateness of its requests and plan for the future.

Lastly, FDA's requests for postmarketing studies put added responsibilities on the drug companies. Therefore, it is reasonable to expect FDA to determine whether or not the studies fulfill the commitments and to notify the companies of the determination.

We recommend that FDA:

- ▶ *establish standards, procedures, or guidelines for individuals responsible for carrying out monitoring and tracking objectives; and*
- ▶ *establish accountability for monitoring, tracking, and bringing commitments to closure.*

Below are some ideas for FDA to consider in order to streamline data management:

- Assign authority to specific personnel for carrying out management objectives. Establish a coordinator with authority to (1) represent all offices involved in monitoring, tracking, and bringing commitments to closure; and (2) ensure that there is a quality control system for the commitments database.

- Reduce the number of documents that have to be researched in order to identify the status of commitments; and use standard notations on these documents to signify how each document affects the status of the commitment.
- Establish descriptive categories for (1) types of studies requested and (2) status of commitments.
- Put the database of postmarketing commitments on-line in the review divisions and allow authorized individuals to update records as soon as an action occurs or a determination is made.

FDA COMMENTS

The FDA agrees with this report's findings and recommendations. A draft directive that establishes procedures and provides guidance is undergoing review within CDER is expected to be finalized by the end of June 1996. (Appendix C contains FDA's comments in full.)

ENDNOTES

1. Accelerated approvals are possible in only two situations:
 - (1) When approval can be based on a drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a drug's effect on a clinical endpoint other than survival or irreversible morbidity. After approval, the applicant would be required to complete adequate and well-controlled clinical studies already underway at the time of approval, to confirm the predictive value of the surrogate endpoint or other indicator. (21 CFR 314.510)
 - (2) When FDA determines that an effective but highly toxic drug can be used safely only if distribution or use is modified or restricted. (21 CFR 314.520)
2. Closure is defined by FDA's Division of Drug Information Resources as:
 - (1) the drug product was not marketed or it was withdrawn from the market (closure would be void if the drug were re-marketed);
 - (2) the drug company was released from all phase iv commitments by FDA;
 - (3) the research was terminated for reasons mutually agreed to by the drug company and FDA; or
 - (4) the research was completed and accepted by FDA as scientifically valid and in fulfillment of the commitment(s).
3. Definition of new molecular entity: The active moiety (component or molecule) has not previously been approved or marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product.
4. The analysis was performed by staff in the Division of Drug Information Resources, Office of Management, Center for Drug Evaluation and Research. It was used in papers presented at (1) the 23rd Annual Meeting of the U.S. Public Health Service Professional Association in Scottsdale, AZ, May 1988, and (2) the 25th Annual Meeting of the Drug Information Association in Boston, MA, June 1989.
5. Review Divisions (as of May 1995): (1) Cardio-Renal, (2) Neuropharmacological, (3) Oncology and Pulmonary, (4) Medical Imaging and Surgical-Dental, (5) Gastrointestinal and Coagulation, (6) Metabolism and Endocrine, (7) Anti-infective, (8) Anti-Viral, (9) Topical Drug Products, and (10) Pilot Drug Evaluation Staff.
6. We used the following method to calculate the time it took FDA to review and determine that studies were acceptable: Out of the 39 studies found acceptable, 25 had submission and determination dates. We calculated the difference between the dates. The time ranged from 5 days to nearly 7 years, for an average of a little over 16 months.

7. We used the following method to calculate the time that studies have been without a determination: Out of 106 studies without a determination, 30 had submission dates. We calculated the difference between those dates and August 31, 1995 which was when the studies' status was most recently updated. The time periods for the 30 studies ranged from 2 to 7-1/2 years.

APPENDIX A

CATEGORIES FOR THE STATUS OF POSTMARKETING COMMITMENTS

On the left are the 15 categories we established in order to analyze status information in FDA's *Phase IV Postapproval Research List*. On the right are the eight categories established by FDA in 1988.

See Appendix B for the number of commitments in each status category as of August 1995.

OIG - 1995

Study Not Begun

- 1.1 Will begin in the future
- 1.2 Company did not agree to conduct study
- 1.3 Company awaiting approval of a supplement application

Study in Progress

- 2.1 Underway
- 2.2 Completed but not yet submitted to FDA
- 2.3 Halted
- 2.4 Perpetual

Study Submitted to FDA

- 3.1 Accepted by FDA
- 3.2 Not accepted by FDA
- 3.3 No determination made by FDA

Released from Commitment

- 4.1 Drug not marketed
- 4.2 Questions answered by other studies
- 4.3 Reason unclear
- 4.4 Study not feasible

Status Unknown

- 5.1 No information

FDA - 1988

- A. Study not begun or status could not be determined
- B. Study in progress
- C. Study is perpetual
- D. Study submitted and FDA determined commitment is met
- E. Study submitted and was rejected by FDA
- F. Study submitted and FDA has not determined if commitment is met
- G. Company released from commitment
- H. Study not completed due to drug not being marketed

APPENDIX B

NUMBER OF PHASE IV COMMITMENTS IN EACH STATUS									
STATUS AS OF AUGUST 1995		YEAR OF DRUG APPROVAL							
		'87	'88	'89	'90	'91	'92	'93	Total
Study Not Begun									
1.1	Will begin in future	1	0	0	3	0	0	9	13
1.2	Company did not agree to conduct study	3	0	1	1	7	2	1	15
1.3	Company awaiting approval of supplement	0	0	0	4	0	3	0	7
Sub-total									35 (9%)
Study in Progress									
2.1	Underway	2	2	4	4	26	29	21	88
2.2	Completed but not yet submitted to FDA	1	5	7	4	14	8	11	50
2.3	Halted	0	1	2	0	7	1	0	11
2.4	Perpetual	0	0	0	0	1	0	0	1
Sub-total									150 (39%)
Study Submitted									
3.1	Accepted by FDA	10	3	3	6	7	8	2	39
3.2	Not accepted by FDA	1	0	0	0	0	0	0	1
3.3	No determination by FDA	10	8	16	17	28	20	7	106
Sub-total									146 (38%)
Company Released from Commitment									
4.1	Drug not marketed	8	0	2	0	0	2	0	12
4.2	Question answered by other studies	1	0	0	0	0	1	0	2
4.3	Reason unclear	0	0	1	0	4	2	0	7
4.4	Study not feasible	0	0	0	0	2	0	0	2
Sub-total									23 (6%)
Status Unknown									
5.1	No information	0	0	0	5	0	4	22	31
Sub-total									31 (8%)
Total		37	19	36	44	96	80	73	385

APPENDIX C

COMMENTS FROM THE FOOD AND DRUG ADMINISTRATION



Memorandum

Date . MAR 28 1996

From Deputy Commissioner for Management and Systems (Acting)

Subject Food and Drug Administration's (FDA) Comments on the Office of Inspector General's (OIG) Draft Report, "Postmarketing Studies of Prescription Drugs," (OEI-03-94-00760), -- ACTION

To

Deputy Inspector General for Evaluation and Inspections

We reviewed the referenced draft report and prepared the attached comments.

The FDA's Center for Drug Evaluation and Research has agreed with the report's recommendation and is beginning to implement it.

If your staff has any questions, please have them contact Jim Dillon on (301) 443-6392.


Robert J. Byrd

Attachment

COMMENTS OF THE FOOD AND DRUG ADMINISTRATION (FDA) ON THE OFFICE
OF INSPECTOR GENERAL (OIG) DRAFT REPORT, "POSTMARKETING STUDIES OF
PRESCRIPTION DRUGS," OEI-03-94-00760, FEBRUARY 1996

General Comments

We appreciate the opportunity to review and comment on the referenced OIG draft report.

The FDA's Center for Drug Evaluation and Research (CDER) agrees with the report's findings and recommendation. CDER wishes to express its gratitude to the OIG evaluators for considering their comments and suggestions on the working draft report.

OIG Recommendation

We recommend that FDA establish standards, procedures, or guidelines for individuals responsible for carrying out monitoring and tracking objectives; and, establish accountability for monitoring, tracking, and bringing commitments to closure.

FDA Comment

FDA concurs. CDER has formed a working group that is carrying out the intent of the recommendation. This working group has drafted a directive that establishes procedures and provides guidance for resolving various issues. The draft directive tentatively entitled, "Tracking Phase 4 Commitments," is undergoing review within CDER and should be finalized by end of June. CDER expects implementation shortly thereafter. The directive will become part of the Manual of Policies and Procedures and will be available for use by all CDER employees.