



Memorandum

Date . JUL I 7 1998

From June Gibbs Brown
Inspector General *June G. Brown*

Subject Review of the Annual Reporting Process for Investigational New Drugs Regulated by
the Food and Drug Administration's Center for Biologics Evaluation and Research
(CIN: A-15-96-50001)

To

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration

The attached final report provides you with the results of our review of the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research's (CBER) process to obtain annual reports for all active investigational new drug applications. We reviewed the efficiency and effectiveness of CBER's process and provided our recommendations for improvements.

On June 5, 1998, we received FDA's comments on our findings and recommendations contained in our draft report dated March 25, 1998. We received additional comments on June 19, 1998.

If you have any questions, please call me or have your staff contact Joseph J. Green, Assistant Inspector General for Public Health Service Audits, at (301) 443-3582. To facilitate identification, please refer to Common Identification Number A-15-96-50001.

Attachment

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**REVIEW OF THE ANNUAL REPORTING
PROCESS FOR INVESTIGATIONAL NEW
DRUGS REGULATED BY THE FDA'S
CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**



**JUNE GIBBS BROWN
Inspector General**

**JULY 1998
A-15-96-50001**

EXECUTIVE SUMMARY

BACKGROUND

The Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) is responsible for overseeing biological products that sponsors develop under investigational new drug applications (INDs). As of September 30, 1997, CBER was overseeing 2,748 active¹ INDs, which allow drug sponsors to conduct research on the safety and effectiveness of promising new drugs. Federal regulations require drug sponsors to submit annual reports to FDA for all active INDs. The reports are essential tools for CBER to oversee the IND process because they provide information pertinent to the safety of research subjects and the integrity of research designs.

OBJECTIVE

Our objective was to evaluate the efficiency and effectiveness of CBER's process to obtain annual reports for all active INDs.

SUMMARY OF FINDINGS

The CBER process for obtaining IND annual reports does not ensure that the reports are consistently received on time or even at all. Federal regulations place the legal responsibility on drug sponsors to submit annual reports, which are valuable tools to ensure patient safety and to monitor clinical trial progress. The CBER's ability to oversee active INDs is diminished when annual reports are not received because it may not be obtaining critical information such as the number of study subjects who died, dropped out of the study, or suffered adverse experiences. From March 1996 to July 1997, CBER significantly reduced the number of outstanding reports from 454 (21 percent) to 267 (13 percent); however, the process still needs to be improved to: further reduce the number of annual reports outstanding; ensure a new backlog does not develop; and improve efficiency in obtaining outstanding reports. While CBER has traditionally given the "policing" of the annual reporting process a low priority in terms of staff time and resources, we believe the agency's investment in this process can result in improved IND oversight.

¹The term "active" describes the administrative status of the IND. An IND becomes active the date FDA receives the IND and remains active until the agency or the sponsor takes an action to change the status by withdrawing, terminating, or inactivating the IND. Sponsors may not conduct clinical investigations using an IND that is withdrawn, terminated, or inactivated.

Our recommendations to the Commissioner of Food and Drugs are to require the Director of CBER to:

- Underscore the importance of annual reports by establishing goals for improving the report collection process and reducing the number of reports outstanding.
- Take a more proactive role in obtaining the annual reports by sending out informational letters to sponsors to remind them of the requirements for annual reports, or posting reminder notices to CBER's website.
- 1 ¶ Further automate the process for collecting outstanding annual reports, including making improvements to the **Biologics** IND Management System (BIMS), which is used to track INDs.
- Improve staff training and written instructions for collecting IND annual reports.
- Redesign the standardized application and amendment cover to facilitate recognition of administrative changes and ensure they are entered into BIMS.
- Consider imposing additional sanctions on IND sponsors who do not submit annual reports.

On June 5, 1998, we received FDA's written comments to the recommendations contained in a draft of this report, issued on March 25, 1998. We received additional comments on June 19, 1998. The FDA provided general and technical comments, which we incorporated throughout the report where appropriate. In terms of our recommendations, the agency basically agreed with the steps we delineated to improve the annual report process, but took exception to imposing additional sanctions on sponsors who do not comply with the regulation requiring the annual report to be submitted to FDA. We discuss FDA's comments and our views in the section entitled, "FDA Comments and OIG Response." Both sets of FDA comments are included in this report as Appendix B.

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INTRODUCTION

BACKGROUND

Role of CBER in Reviewing New Biological Drugs

The FDA's CBER oversees the development of new biological products used to treat and prevent a variety of illnesses, including such conditions as AIDS and cancer. A biological product, or biologic, is any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries in humans. Biologics include vaccines, blood products, therapeutic products, allergenic extracts, and other related products. Before a new biological product can be tested on human subjects, the product's sponsor must submit an IND² to CBER requesting authorization to administer an investigational drug or biological product to humans. During Fiscal Year (FY) 1997, CBER received 442 new INDs; and as of September 30, 1997, it was responsible for overseeing 2,748 active INDs. According to data provided by CBER, for most of the biological products approved between 1991 and 1996, the average duration for the IND phase was: 50 months for the Office of Therapeutics Research and Review (OTRR); 51 months for the Office of Vaccines Research and Review (OVRR); and 60 months for the Office of Blood Research and Review (OBRR).

After receiving an IND, CBER has 30 days to assess the safety of the IND. At the end of this period, the IND is considered in effect and the sponsor may begin conducting clinical investigations. If problems are noted with the application, however, CBER may put the IND on clinical hold, which is an order to the sponsor to delay or suspend clinical investigations.

Unless the post-approval clinical studies continue, CBER monitors the progress of the IND until it is withdrawn, inactivated, or terminated. Before the sponsor can market a biological product in the United States, it submits data developed during the IND phase to CBER in two types of applications: (1) the product license application (PLA), which allows commercial use of the product; and (2) the establishment license application (ELA), which allows the manufacture of the product at a specific facility. The CBER is beginning to replace the PLA and ELA with a new Biologics License Application (BLA). The FDA must approve both the PLA and ELA, or a BLA, before the product can be marketed in this country.

Three CBER offices are responsible for IND reviews: OVRR, OTRR, and OBRR. Each incoming IND is assigned to an interdisciplinary review team that includes experts in areas

² Although the term IND is used throughout this report, CBER also reviews investigational device exemptions (IDE) for medical devices. Although different regulations apply to IDEs, the review processes is similar to that for INDs. Since CBER reviews far more INDs than IDEs, the term IND will be used throughout the report to refer to both INDs and IDEs.

such as product (manufacturing process and characterization, stability, etc.), clinical design, pharmacology, microbiology and toxicology. Depending on the product and phase of study, reviewers with expertise in areas such as statistical design, facilities, and device engineering may be added to the team. One member of the team is designated as the primary reviewer. In addition to reviewers, each office employs consumer safety officers (CSOs) who generally serve as the administrative/coordinating members of the IND review team. The CSOs perform various duties which typically include: reviewing technical, administrative, and regulatory aspects of IND/PLA/BLA applications, and evaluating and implementing administrative and regulatory actions in relation to applications and amendments.

IND Oversight Tools

According to Title 21 Code of Federal Regulations (C.F.R.), section 312.22(a): “FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety”³

The CBER accomplishes these objectives by monitoring the progress of all active INDs. Its monitoring process contains numerous tools to ensure these goals are met, including:

- a 30-day safety review that must be passed before the product can be given to humans;
- requirements for an Institutional Review Board (IRB)⁴ to ensure the protection of the rights and welfare of human subjects involved in IND studies;

³ Phase 1 studies are conducted to determine the metabolism and pharmacologic action of the drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. Phase 2 studies are generally conducted to evaluate the effectiveness of the drug and further evaluate safety. Phase 3 studies are conducted to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk of the drug. Phase 2 and 3 studies involve more subjects than phase 1 studies.

⁴ An Institutional Review Board is a group formally designated by an institution to review biomedical research involving human subjects, primarily in order to assure the protection of the rights and welfare of the subjects.

- reporting requirements for certain adverse experiences' (i.e., those that would constitute hazards, contraindications, side effects, precautions, or deaths) experienced by research subjects, and changes to research study designs;
- annual reports, submitted to CBER in the form of amendments to the IND, which summarize the progress of the IND investigation during the prior year. Annual reports are to contain information necessary for CBER to assess the IND's progress including: the number of subjects who enrolled, dropped out, or died; summaries of adverse experiences, safety reports, significant manufacturing or microbiological changes; and the investigational plan for the coming year; and
- meetings with and telephone calls to sponsors.

In terms of data management, CBER uses a relational data base--BIMS--to track INDs throughout their life cycle, including the submission of original INDs, subsequent amendments, correspondence, and review activities. A standard BIMS report, "INDs with Overdue Annual Reports," assists CSOs in identifying and obtaining outstanding annual reports. The CBER is currently developing a new biologics IND information system known as the "Regulatory Management System" (RMS). Current data from the Biologic Regulatory Management System (BRMS), which tracks PLAs, ELAs, and BLAs, will be converted to RMS. According to CBER, BIMS will be integrated into RMS in the next phase of development.

OBJECTIVE, SCOPE, AND METHODOLOGY

Objective

Our objective was to evaluate the efficiency and effectiveness of CBER's process to obtain annual reports for all active INDs.

Scope

We initiated a review of the IND process in response to a highly publicized incident involving the kidney transplant drug, anti-lymphocyte globulin (ALG), which the University of Minnesota sold commercially without FDA approval. In this case, the university violated numerous IND regulations, including those pertaining to annual reporting, adverse experience reporting, and commercialization of an IND. Although the ALG IND was in effect for

⁵ IND sponsors are required to notify FDA of any adverse experiences associated with the use of the drug that are both serious and unexpected, in a written safety report, within 10 working days of the sponsor's receipt of such information. Sponsors are also required to notify FDA by telephone of any unexpected fatal or life-threatening experience associated with the use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information.

22 years, the university did not, according to cognizant FDA officials, conduct adequate studies to support a PLA or BLA. Had the university submitted routine annual reports, we believe FDA would have been in a better position to monitor the ALG IND and guide it toward a successful PLA or BLA.

We obtained an understanding of the internal controls, including monitoring tools, that CBER has in place to ensure it meets its objectives of assuring the safety of study subjects and to ensure that studies are adequate to lead to an approval decision. We performed a risk assessment to identify the factors that could prevent CBER from meeting its objectives and determined the controls that were in place to minimize these risks. As a result of our understanding of the internal control system and our risk assessment, we focused our review on the annual reporting process. Our review also included gaining an understanding of the controls in place to track IND documents and information throughout the IND process; including a tour of the Document Control Center (DCC), meetings with officials from CBER's Regulatory Information Management Staff (RIMS), and review of BIMS manuals. .

Our review did not include a substantive review of the contents of the IND annual reports submitted to CBER.

Methodology

We reviewed pertinent laws, regulations and CBER policies and procedures related to INDs; attended briefings on the IND process presented by FDA; and interviewed 17 reviewers, 9 CSOs, 2 RIMS members, and 2 DCC staff.

We analyzed the data generated by CBER's BIMS to determine the number and percentages of annual reports outstanding: at the end of FYs 1993-1996; at the beginning of our review; and as of July 1997.

We also analyzed the data from the start of our review, March 1996 through July 1997 (our most current data) to determine how long annual reports remain outstanding and whether CBER promptly issues reminder, pre-termination, and termination letters when sponsors do not submit annual reports.

We performed our review in accordance with generally accepted government auditing standards. Our work began in 1996 and was suspended in March 1997, due to other priorities. We resumed work on this review from July to September 1997. Our work was performed in FDA offices located in Rockville, Maryland:

RESULTS OF REVIEW

The CBER process for obtaining IND annual reports does not ensure that the reports are consistently received on time or even at all. Federal regulations place the legal responsibility on drug sponsors to submit annual reports, which are valuable tools to ensure patient safety and to monitor clinical trial progress. The CBER's ability to oversee active INDs is diminished when annual reports are not received because it may not be obtaining critical information such as the number of study subjects who died, dropped out of the study, or suffered adverse experiences. From March 1996 to July 1997, CBER significantly reduced the number of outstanding reports from 454 (21 percent) to 267 (13 percent); however, the process still needs to be improved to: further reduce the number of annual reports outstanding; ensure a new backlog does not develop; and improve efficiency in obtaining outstanding reports. While CBER has traditionally given the "policing" of the annual reporting process a low priority in terms of staff time and resources, we believe the agency's investment in this process can result in improved IND oversight.

CRITERIA) ANNUAL REPORTS PROVIDE KEY INFORMATION FOR CBER IND OVERSIGHT

Federal regulations require sponsors to submit annual reports to FDA on the progress of their IND studies. These annual reports are valuable tools used by CBER to ensure the safety of research subjects and guide research toward eventual approval of a PLA or BLA. Because the annual reports are essential, CBER has standard operating procedures⁶ requiring the collection of reports that are not received.

Annual Reports are Required by Regulation

The Code of Federal Regulations (C.F.R.), Title 21, Part 312.33, requires sponsors to submit to FDA a report on the progress of the IND investigation within 60 days of the anniversary date that the IND went into effect, and annually thereafter. The C.F.R. specifies the information to be contained in the annual report, including: the number of subjects who enrolled, dropped out, or died; summaries of adverse experiences, safety reports, significant manufacturing or microbiological changes; and the investigational plan for the coming year. The annual report is the primary mechanism to provide much of this information to CBER.

⁶ In its comments regarding our draft report, FDA clarified that the guidance used during the period of our review was developed for use by CBER's OTRR. While we documented that OTRR's SOPs were used Center-wide, FDA said they should not be considered a Center-wide SOP. The agency pointed out in its comments that CBER is developing Center-wide SOPs.

Annual Reports Assist CBER in Meeting **its** Regulatory Objectives

Annual reports are valuable tools that assist CBER in meeting its safety and monitoring objectives, as designated by the C.F.R. The annual reports provide essential data that reviewers need to identify safety problems with INDs and allow an additional opportunity for reviewers to learn about adverse experiences. The annual report also helps CBER meet its monitoring objectives by giving reviewers the opportunity to examine data regarding the prior year's progress and to assess studies planned by the IND sponsor for the coming year. Such review enables CBER staff to identify problems and suggest solutions to the sponsor before resources are wasted on studies that will not be sufficient to substantiate a product license.

CBER has a process for collecting outstanding annual reports

The CBER has procedures for staff to follow to collect reports that are not submitted to the agency. According to CBER's standard operating procedures, the appropriate staff, which are commonly the CSOs, are to review the monthly BIMS report, "INDs with Overdue Annual Reports," to identify overdue reports within their offices. For each outstanding report, the CSO is to check the IND file to confirm that the report was not received. If the report is not in the file, the CSO is to send a reminder letter to the sponsor stating the requirement for annual reports and requesting the sponsor to submit the absent report within 30 days. If a report is not received within 30 days, the CSO is to send a pre-termination letter alerting the sponsor that the IND will be terminated if the report is not received. If a response is still not received after another 30 days, the CSO is to send a termination letter to the sponsor stating that its IND has been terminated. We observed that CBER's standard operating procedures, while providing specific steps for obtaining outstanding reports, do not specify the time frames within which the letters are to be sent.

(CONDITION) CBER HAS REDUCED THE NUMBER OF LATE ANNUAL REPORTS. BUT MANY REMAIN OUTSTANDING

While CBER has significantly reduced the number of late annual reports since FY 1993, there remains a significant number of reports outstanding, some of which **are overdue** by more than 10 years. Further, the improvement was largely due to the CSOs' devoting more time than usual to collecting the reports, rather than from improvements to the report collection process. The process is cumbersome, and the CSOs are not able to keep up with the workload. Changes to the process should be made to: (1) ensure that the number of annual reports outstanding continues to decline; (2) prevent possible increases in the number of outstanding annual reports in the future; and (3) reduce the amount of effort required by the CSOs.

Annual Reporting Rates are Improving

The CBER has significantly reduced the number of outstanding annual reports since 1993, with the most dramatic improvements occurring since the start of our review. As shown by the

chart below, CBER reduced the number of outstanding annual reports to 267, or 13 percent. This is down from 454 reports, or 21 percent, in March 1996; and 689 reports, or 32 percent, at the end of FY 1993.

<i>Date</i>	<i>Number of Reports Outstanding</i>	<i>Number of Active INDs</i>	<i>Percentage of Reports Outstanding</i>
<i>July 1, 1997</i>	267	2093	13
<i>March 1, 1996</i>	454	2179	21
<i>October 1, 1995</i>	442	2099	21
<i>October 1, 1994</i>	536	2047	26
<i>October 1, 1993</i>	689	2141	32

Despite the improvement, we identified numerous sponsors that have not reported in years. For example, at the outset of our review in March of 1996, there were 58 INDs for which sponsors had not reported to CBER in 10 years or more. As of July 1, 1997, CBER still had not received reports for 15 of them. In the worst instance, a sponsor had not submitted an annual report in almost 19 years. The following chart shows the distribution of INDs with outstanding annual reports, grouped by years elapsed since submission of the last annual report.

<i>As of:</i>	<i>1 < 2 years</i>	<i>2 < 5 years</i>	<i>5 < 10 years</i>	<i>Over 10 years</i>	<i>Indeterminate*</i>	<i>Total Reports Outstanding</i>
<i>July 1, 1997</i>	193	54	4	15	1	267
<i>March 1, 1996</i>	167	156	63	58	10	454

* The data was not readily available for these INDs because CBER had not entered into BIMS the date of the last annual report. According to CBER, these were older INDs that began before the BIMS system was upgraded in December 1993. The CBER, therefore, has not received an annual report for these INDs since at least 1993. As of March 1, 1996, CBER still had not entered the correct data for these 10 INDs into the BIMS system.

We also noted several instances where sponsors failed to submit annual reports for multiple INDs. For example, we brought to CBER's attention the case of one sponsor with

26 outstanding IND annual reports. At the close of our review, this sponsor still had 21 annual reports outstanding.

The CSOs cannot maintain the annual report workload

The CBER has reduced the number of outstanding annual reports by increasing employee collection efforts; however, it has not improved the process for obtaining outstanding annual reports. As a result, the CSOs cannot keep up with the workload, and they acknowledge that the backlog of outstanding annual reports grows whenever other priorities take precedence. For example; our review of July 1, 1996 to June 30, 1997, BIMS data show that, from the date the annual report became overdue, it took CSOs an average of 20 months to issue the initial reminder letter. While there is currently no time frame for issuing the initial reminder letter, we believe almost 2 years is an excessive period.

The CSOs also have difficulty adhering to the requirement to send out pre-termination and termination letters to sponsors failing to submit their annual reports. According to CBER's procedures regarding collection of outstanding annual reports, the CSOs should send out pre-termination letters 30 days after the reminder letter, if the annual report still has not been received. However, based on pre-termination letters issued between July 1, 1996 and June 30, 1997, 52 percent of the letters took over 90 days to be issued. The CBER procedures state that termination letters should be sent out 30 days after the pre-termination letter, if no response is received. We noted 26 instances where INDs still had not been terminated a year after the pre-termination letter was sent.

Terminating the IND is the only form of sanction CBER imposes when a sponsor does not comply with annual reporting regulations. Although CBER has terminated INDs for failure to submit annual reports, CBER officials told us they are reluctant to terminate promising INDs because to do so could prevent subjects from receiving possibly beneficial medication and halt development of a potentially useful drug. Officials are also reluctant to terminate INDs that are cross referenced as support for other INDs, because that would jeopardize the status of INDs that are in compliance. Further, some CBER officials do not consider failure to submit annual reports an offense serious enough to justify termination.

(EFFECT) CBER'S OVERSIGHT OF INDs IS DIMINISHED WHEN ANNUAL REPORTS ARE NOT RECEIVED

When CBER does not receive IND annual reports, it may not receive critical information needed to ensure the continued safety of study subjects and monitor the IND's progress. Conversely, when reports are received, CBER has used the information contained in them to prevent, serious safety problems and identify study deficiencies before the sponsors wasted resources on insufficient studies, which would ultimately result in increased approval times. For these reasons, CBER should receive an annual report for every IND.

Missing Annual Reports Represent Missed Opportunities

When CBER does not receive IND annual reports, reviewers may not have access to critical information essential to monitoring patient safety, such as the number of subjects who died, suffered an adverse experience, or dropped out of the study, as well as valuable summary data and tabulations necessary to identify patterns and trends. Without this information, the CBER reviewers may not be in a position to identify safety problems with an IND, and in turn, require the sponsor to take action before adverse experiences occur. In addition, without the annual reports, reviewers may not be able to determine if the studies being conducted and planned for the upcoming year will be adequate to eventually support a PLA or BLA.

Annual reports may be the only information CBER obtains for an IND for the entire year, particularly from IND sponsors/investigators for small companies. The CBER rarely uses on-site inspections to obtain knowledge about ongoing IND studies for two reasons. First, resources for reviewing INDs are limited since FDA elects not to use funds provided by the Prescription Drug User Fee Act of 1992.⁷ Second, clinical study inspections are given a low priority because only about 30 percent of INDs proceed to the marketing application phase of development. Since CBER generally does not obtain knowledge of the ongoing IND studies through site visits, and may not receive any other information from the sponsor during the year, the information provided in the annual reports is essential for CBER to carry out its monitoring role.

The annual report serves other important functions, which are not met when the reports are outstanding. For example, when reports are not received, there can be gaps in the knowledge of the sponsor, IRB, and CBER reviewers, with regard to the progress of the IND. The reports: (1) serve as a valuable self-assessment for the sponsors, who often gain new insights from preparing the reports; (2) may assist IRBs in monitoring INDs⁸; (3) bring the CBER reviewers up-to-date on any adverse experiences or protocol changes that may not have been reported during the year; (4) provide information necessary to perform an assessment of the risks to study subjects; and (5) serve as a permanent summary of past, current, and planned studies under an IND, thereby easing transitions when the IND is transferred from one reviewer to another and one sponsor to another.

⁷ The Prescription Drug User Fee Act of 1992 (PDUFA), Public Law 102-571, authorized revenues from fees paid by the pharmaceutical industry to expedite FDA's review of human drug applications. During the early period of our review, FDA officials told us that PDUFA funds could not be used to cover the IND phase. In its comments regarding our draft report, FDA stated that while PDUFA funds are available for the IND phase, the agency chooses to apply these funds for other priorities, such as expediting the review and approval process so that new drugs can be introduced on the market at an earlier date.

⁸ Although Federal regulations do not require the sponsor to submit the **annual** report to its IRB, CBER reviewers informed us **that the IRBs** frequently receive the reports from sponsors/investigators and rely on them to help monitor the IND.

Annual Reports Prevent Problems

The CBER has used the annual reports to identify safety problems that could result in unnecessary death or injury to study subjects. For example, annual reports:

- Alerted FDA to two separate INDs where patients were receiving unsafe dosages of medication. The FDA required the sponsors to take precautions to prevent patients from receiving further unsafe dosages. An FDA inspection of one of the sponsors uncovered numerous additional problems.
- Alerted a reviewer to the fact that a sponsor's IND product inventory had reached its expiration date. The FDA required the sponsor to obtain a supply of fresh product.
- Alerted reviewers to several IND sponsors that were not reporting adverse experiences during the year, as required by regulation. The CBER would not have learned about these adverse experiences if not for the annual reports.
- Led to several for-cause inspections,⁹ eventually resulting in warning letters to the sponsors indicating that the sponsors were out-of-compliance with IND regulations. One of the inspections resulted in an IND being put on clinical hold.
- Alerted the IND sponsor of adverse event patterns that were not evident to individual investigators located at various sites. These adverse event patterns indicated that there were product safety problems. Upon learning this, the sponsor withdrew the IND.

Several CBER reviewers we interviewed also informed us of numerous instances where their review of the annual report revealed that proposed studies would not be adequate to eventually support a PLA or BLA. The reviewers then suggested improvements to ensure the study would be properly designed. In these cases, if the reviewers had not received the annual reports, sponsors could have wasted years conducting studies that would not be adequate to obtain product approval, ultimately increasing the time to get new treatments on the market.

⁹ CBER initiates a "for cause" inspection when it determines there is a need to investigate a particular issue, typically involving issues related to the safety and rights of study subjects, significant violations of the law, and complaint resolution.

(CAUSE) POLICING ANNUAL REPORT COLLECTION
HAS NOT BEEN A CBER PRIORITY

Among CBER's responsibilities, the policing of the reporting process is a low priority. Because so many drug sponsors are delinquent in filing the reports, we believe that devoting additional resources to this effort is necessary. Consistent with the low priority assigned to this policing effort, we identified numerous inefficiencies in the reporting process. Further, CBER has not made it a priority to sanction the sponsors that do not comply with the annual reporting requirement.

Low Priority Leads to Process Inefficiencies

The low priority CBER has accorded to the annual reporting process appears to be associated with several inefficiencies, including:

- Absence of time frames for CBER staff with regard to collection procedures. Even though there is a procedure for the CSOs to follow with regard to collection of outstanding reports, there are no established time frames for sending collection letters. The CSOs we interviewed indicated that they only attempt to collect the outstanding reports "when there is extra time."
- Except for the instructions in the acknowledgment letter CBER sends to sponsors when a new IND is received, CBER currently does not take proactive measures to ensure that the reports are sent in on time and in accordance with regulations contained in C.F.R., Title 21, Part 312.33.
- The CBER has not fully automated and streamlined the report collection effort, resulting in a cumbersome process that is difficult for the CSOs to maintain. For example:
 - Not all of the CSOs take advantage of the automated mailing system in DCC. One of CBER's offices still prepares envelopes and necessary paperwork by hand.
 - The BIMS does not contain boiler plate pre-termination and termination letters to facilitate production of these letters.
 - The CSOs do not receive monthly hard copies of the BIMS report "INDs with Overdue Annual Reports" to act as a trigger to send out letters for the overdue reports.

- The BIMS allows a 60-day grace period before outstanding reports appear on the “INDs with Overdue Annual Reports” list. The CBER added this period to allow for mail delays and delays in in-house processing.
- Inadequate training: The CBER has not devoted sufficient time to training the CSOs to ensure they are all abreast of the most efficient methods available for obtaining the annual reports.
- The BIMS data is not always up to date, which results in reports being listed as overdue, when in fact no report is due because the IND has been withdrawn, closed, or inactivated. While these problems are rare, such inaccuracies require the CSOs to spend additional time checking the IND files to ensure the BIMS data is correct. Many of the inaccuracies in BIMS occur because administrative changes crucial to tracking the IND, such as changes of sponsor, sponsor address, and requests for withdrawal are often buried in bulky amendments where they can easily be missed by CSOs. Information is buried in the amendments because the standard cover sheet for IND amendments does not contain fields for sponsors to clearly identify many of these administrative changes. In addition, CBER does not always receive cover sheets for amendments because they are not required for amendments, and CBER does not emphasize their submission.

Low Priority Leads to Minimal Penalties For Non-Compliance

Because of the low priority accorded to collecting outstanding annual reports, CBER does not routinely impose penalties on sponsors who fail to submit the reports. Currently, the only sanction CBER imposes on sponsors who fail to submit annual reports is terminating the IND; however, this is a serious step that could prevent research subjects from receiving beneficial medication and halt development of a potentially useful drug.

Some of the CBER officials we interviewed do not consider failure to submit annual reports an offense serious enough to justify terminating an IND, partly because they believe reviewers have other opportunities to obtain some of the information presented in the annual reports. These other opportunities include: adverse experience reports, protocol amendments, meetings with sponsors, and telephone contacts. While such opportunities are useful for monitoring INDs, the annual report, with its specific regulatory requirement, represents the most consolidated form of communication between the sponsor and CBER.

CONCLUSIONS

The CBER process for obtaining IND annual reports does not ensure that the reports are consistently received on time or even at all. Federal regulations place the legal responsibility on drug sponsors to submit annual reports, which are valuable tools to ensure patient safety

and to monitor clinical trial progress. The CBER's ability to oversee active INDs is diminished when annual reports are not received because it may not be obtaining critical information such as the number of study subjects who died, dropped out of the study, or suffered adverse experiences. From March 1996 to July 1997, CBER significantly reduced the number of outstanding reports from 454 (21 percent) to 267 (13 percent); however, the process still needs to be improved to: further reduce the number of annual reports outstanding; ensure a new backlog does not develop; and improve efficiency in obtaining outstanding reports. While CBER has traditionally given the "policing" of the annual reporting process a low priority in terms of staff time and resources, we believe the agency's investment in this process can result in improved IND oversight.

RECOMMENDATIONS

The following recommendations are presented in broad terms. The recommendations requiring further detail are listed in Appendix A.

We recommend that the Commissioner of Food and Drugs require the Director of CBER to:

1. Establish goals for the annual reporting process

To underscore the importance of annual reports, CBER officials should establish goals for improving the report collection process and reducing the number of outstanding reports. Within the context of CBER's resources and priorities, management should establish time frames for each of the collection procedures in the standard operating procedure "Dunning for IND Annual Reports and Deactivating INDs." For example, the first reminder letter could be sent out within 60 days of the date the report was due; pre-termination letters could be sent out within another 90 days if there is no response to the reminder letter; and termination letters could be sent out within another 90 days if there is no response to the pre-termination letter.

The CBER management should monitor BIMS reports to ensure goals are-being met, and periodically review a listing of overdue INDs by sponsor in order to identify sponsors that have a pattern of non-compliance with reporting requirements.

2. Become more proactive in obtaining annual reports

The CBER should take a more proactive role in obtaining the annual reports by sending out informational letters or posting notices to its website to: remind sponsors of the requirements for annual reports; address any other common compliance problems; and educate sponsors about any changes to regulations. This proactive approach would likely result in more annual reports being submitted, thereby reducing the need to collect outstanding reports. The letters should explain the regulations, and why it is in the sponsors' best interest to submit the report to FDA.

3. Improve automation related to the annual reporting process

The CBER should further automate the report collection process for outstanding annual reports to ensure that the process runs more efficiently. (See detailed suggestions in Appendix A.)

4. Improve outstanding report collection procedures and training

The CBER CSOs should receive standardized training, with updates as necessary, to keep them abreast of the annual report collection process. The CSOs from each office who are responsible for collecting outstanding reports should meet quarterly so that the best practices for collecting outstanding reports can be identified and adopted by all CBER offices.

5. Redesign forms to improve integrity of BIMS data

The standard application and amendment cover sheet, Form FDA 1571, "Investigational New Drug Application," should be redesigned to facilitate recognition and entering of administrative changes. This improvement will also bolster the integrity of the BIMS data. (See detailed suggestions in Appendix A.)

6. Consider additional sanctions for sponsors who do not submit annual reports

Currently IND termination is the only sanction CBER imposes on sponsors who do not submit annual reports. The CBER should develop other sanctions for noncompliant sponsors. (See detailed suggestions in Appendix A.)

FDA COMMENTS AND OIG RESPONSE

On June 5, 1998, we received FDA's written comments to the recommendations contained in a draft of this report, dated March 25, 1998. The FDA provided additional comments on June 19, 1998. The FDA provided general and technical comments, which we incorporated where appropriate. The agency also commented on each recommendation, as discussed below. Both sets of FDA comments are included in this report as Appendix B.

The FDA generally concurred with our recommendations to: establish goals for the annual reporting process; become more proactive in obtaining annual reports; improve the automation, procedures, and training related to the annual reporting process; and redesign certain forms to improve the integrity of BIMS data. In its comments, FDA detailed numerous steps it has taken, or plans to take, to address these recommendations.

The FDA did not agree with our recommendation to consider the legal feasibility of imposing additional sanctions for sponsors who do not submit annual reports, citing the intensive resources that would be involved "given the number of noncompliant facilities." In additional comments submitted to OIG on June 19, 1998, to clarify some of our questions, FDA

committed to evaluating existing authorities, resources, and mechanisms available to enhance compliance with the annual reporting regulatory requirement. We continue to believe that additional sanctions, even those requiring regulatory changes, should be considered to help reduce the number of noncompliant sponsors. Funds obtained from civil monetary penalties, for example, would be useful in off-setting the cost of FDA's IND oversight.

APPENDICES

SUGGESTIONS FOR IMPLEMENTING RECOMMENDATIONS 3, 5, AND 6

Recommendation # 3: Improve automation related to the annual reporting process

The CBER should implement automation improvements to the outstanding report collection process so that the process runs more efficiently. Improvements should:

- Ensure that all CSOs use the automated mailing system in the Document Control Center. Currently one office still prepares the envelopes and necessary paperwork manually.
- Add boiler plate pre-termination and termination letters to the BIMS system.
- Routinely generate and provide CSOs with a hard copy of the BIMS monthly list of “INDs with Overdue Annual Reports” to act as a trigger to send out letters for the overdue reports.
- Eliminate the 60-day grace period before outstanding annual reports appear on the “INDs with Overdue Annual Reports” list.

Recommendation # 5: Redesign forms to improve integrity of BIMS data

The standard application and amendment cover sheet, Form FDA 1571, “Investigational New Drug Application,” should be redesigned to facilitate recognition and entering of administrative changes. This improvement will also bolster the integrity of the BIMS data. The redesigned form should:

- Include a box to check off if the sponsor, sponsor name, or sponsor address has changed since the last submission. A box for “request for inactivation and withdrawal” should be added under item number 11 to ensure that INDs do not remain open after sponsors withdraw them.
- Be retitled to reflect that it should be completed for IND amendments as well as applications. The title of the form should be changed to “Investigational New Drug Application or Amendment.” Currently, all sponsors do not use the form with amendment submissions. Submission of Form FDA 1571s could be encouraged on CBER’s website or included in suggested sponsor letters sent out to remind sponsors of annual report requirements.
- Include in the certification, a statement as follows: “I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or

administrative penalties.” Such a statement is particularly important since FDA relies on an honor system with regard to INDs.

Recommendation # 6: Consider the legal feasibility of imposing sanctions for sponsors who do not submit annual reports. For example:

- Impose civil monetary penalties, issue warning letters, initiate inspections, or put INDs on clinical hold until the sponsors are brought into compliance.
- Provide monetary incentives for sponsors to submit annual reports, for example, informing Federal funding agencies of sponsors who have not complied with FDA’s annual reporting requirements, and requesting agencies to consider withholding of Federal funds to noncompliant entities.
- Conduct inspections of the sponsor’s site to obtain information normally contained in the annual report, and charge the sponsor for the cost of the inspection.



Memorandum

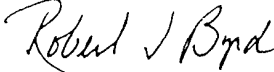
Date: **JUN - 5 1998**

From: Deputy Commissioner for Management and Systems

Subject: Review of the Annual Reporting Process for Investigational New Drugs Regulated by the Food and Drug Administration's Center for Biologics Evaluation and Research.
(CIN: A-1 S-96-50001)

To: June Gibbs Brown
Inspector General

Thank you for the opportunity to review and comment on Office of Inspector General draft report, "Review of the Annual Reporting Process for Investigational New Drugs Regulated by the Food and Drug Administration's Center for Biologics Evaluation and Research." FDA agreed with most of the recommendations. In instances where we did not agree with a recommendation, our comments provide the basis for the disagreement.


Robert J. Byrd

Attachment

AGENCY COMMENTS ON THE OFFICE OF INSPECTOR GENERAL DRAFT REPORT :
REVIEW OF THE ANNUAL REPORTING PROCESS FOR INVESTIGATIONAL
NEW DRUGS REGULATED BY THE FOOD AND DRUG ADMINISTRATION'S
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

General Comments

Please note that the acronym "CBER" mentioned throughout the report represents "The Center for Biologics Evaluation and Research" and is therefore not necessary to be referred to as "the CBER"

Throughout the document, references are made to the "report collection system." The word "system" makes it somewhat confusing as to whether the discussion is in regard to the process or the BIMS. Reference to the report collection "process" would better define the operations.

Technical Comments

Introduction - Background

Page 1, first paragraph: Use of the terms "therapeutics", "vaccines" and "blood products" represent a very narrow scope of products regulated by the product review offices in CBER. Replace with: "...the average duration for the IND phase for each office in CBER was: 50 months for the Office of Therapeutics Research and Review; 51 months for the Office of Vaccines Research and Review; and 60 months for the Office of Blood Research and Review."

Page 1, second paragraph: "If problems are noted with the application, however, CBER puts the IND on hold." CBER may put the IND on hold. As per 21 CFR 312.42, the regulations only allow clinical holds for certain specific problems (i.e. insufficient information to assess risks to subjects or clearly deficient protocol design).

Page 1, third paragraph: Replace first sentence with: "Unless the post-approval clinical studies continue, CBER monitors the progress of the IND until it is withdrawn, inactivated, or terminated."

Page 1, last line: Revise to read as: "...experts in areas such as product (manufacturing process and characterization, stability, etc.), clinical design,..."

Page 1, footnote 2: Revise to read as: "Although the term IND is used throughout this report, CBER also reviews investigational device exemptions (IDEs) for medical devices. Although different regulations apply to IDEs, the review process is similar to that for INDs. Since CBER reviews more INDs than IDEs, the term IND will be used throughout the report to refer to both INDs and IDEs."

IND Oversight Tools

Page 2, first bullet: Revise to read as: "A 30 day safety review that must be passed before the product can be given to humans."

Page 2, second bullet: The use of the word "development" is incorrect. As per 21 CFR Part 56, the definition of IRB "means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects." Since studies done under an IND are often performed at many institutions, getting agreement from all of the IRBs on the appropriate development of the IND would be a monumental task.

Page 2, third bullet: Revise to read as: "(i.e. those that would constitute hazards, . ..)"

Page 2, footnote 5: Revise to read as: "...of any adverse experience associated with use of the drug..."

In addition to the information in footnote 5, as per 21 CFR 312.32 (c)(2), "the sponsor shall notify FDA by telephone of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information."

Page 3: Revise last two sentences to read as: "CBER is currently developing a new, comprehensive biologics information system known as the "Regulatory Management System" (RMS). Current data from the Biologic Regulatory Management System (BRMS), which tracks BLAs and PLAs, will be converted to RMS. BIMS will be integrated into RMS in the next phase of development."

(Criteria) Annual Reports Provide Key Information for CBER IND Oversight

Page 5, second paragraph: "CBER has standard operating procedures requiring the collection of reports that are not received." The SOP referred to here and other places in this document is not an official center-wide SOP, but rather an SOP developed by OTRR (which receives about 60% of the Center's INDs) shortly after the reorganization. Although OTRR's SOP has been used as guidance by the other product review offices, CBER is developing a center-wide SOP.

Report Tables

Page 7, second table, footnote: BIMS went into production in the spring of 1991 and was originally referred as DTS. The upgrade to BIMS occurred in December 1993.

Page 7, second table, "Indeterminate" column: It is unclear if the "indeterminate" INDs are really INDs for which no annual report had ever been received. Is the reduction in the "indeterminate" data from 10 to 1 due to deactivation of the INDs, or annual report submission

dates being entered into the system'!

Missing Annual Reports Represent Missed Opportunities

Page 9, second paragraph: PDUFA funds were restricted to cover only the review period after the initial 30 day period. Funds procured under The Food and Drug Administration Modernization Act of 1997 cover the whole review period of an IND including the initial 30 days.

Page 9, footnote 7: Revise to read as: "receive the reports from sponsor/investigator and rely..."

Annual Reports Prevent Problems

Page 10, second bullet: Replace "expired" with "reached its expiration date"

(Cause) Policing Annual Report Collection Has Not Been a CBER Priority

Page 11, second bullet: 21 CFR 312.33 defines the sponsor's legal responsibility to submit annual reports in a timely manner (within 60 days of the anniversary date that the IND went into effect).

Page 11, third bullet, fourth sub-bullet: The "two month" period of time is calculated and executed in BIMS as a 60 day period. This 60 day grace period in BIMS was created to allow for mail delays and delays in in-house processing and data entry.

Appendix

Recommendation 3, fourth bullet: The "two month" period of time is actually calculated and executed in BIMS as a 60 day period.

Recommendation 5, first bullet: Replace "activation" with "inactivation"

RECOMMENDATIONS

Recommendation #1 - Establish goals for the annual reporting process.

CBER agrees with the recommendation that goals for improving the report collection process and reducing the number of outstanding reports should be established. However, time frames for establishing these goals should be within proper perspectives based upon current resource constraints and other priorities.

Recommendation #2 - Become more proactive in obtaining annual reports.

CBER concurs in part with this recommendation. An IND sponsor has a legal obligation to submit annual reports in a timely manner (within 60 days of the anniversary date that the IND went into effect) as required by 21 CFR 312.33. A copy of this regulation is included in the Annual Report Request letters. CBER also includes copies of 21 CFR 312. which discusses the IND regulations and sponsor responsibilities, with each IND acknowledgment letter. In addition, CBER's Managed Review Committee is evaluating the development of standard language that would be incorporated into all informational request correspondence to sponsors reminding sponsors to submit annual reports.

Recommendation #3- Improve automation related to the annual reporting process.

CBER agrees with the recommendation that the report collection process be further automated. CBER currently is developing a new comprehensive biologics information system known as the "Regulatory Management System" (RMS). Current data from the Biologic Regulatory Management System (BRMS), which tracks BLAs and PLAs, will be converted to RMS. BIMS will be integrated into RMS in the next phase of development. There will be a user friendly interface so that all staff will be able to use this resource effectively. CBER will develop mechanisms to assess the needs of staff and to determine the adequacy of systems on an ongoing basis. CSOs in product review offices have the capability of generating the "INDs with Overdue Annual Reports", and are individually responsible for generating the report and taking action.

Please note that all CSOs in all offices have access to the automated mailing system in the Document Control Center. However, an office can choose to prepare its own envelopes manually if it finds that process to be more efficient.

CBER believes that time frames should be within proper perspectives based upon current resource constraints and other public health related priorities.

Recommendation #4 - Improve outstanding report collection procedures and training.

CBER agrees with the recommendation. The Center has established a new committee to evaluate reviewer training needs and consider possible enhancements to ensure all review staff are appropriately trained. CBER agrees that training is an important tool to insure consistent and thorough application reviews throughout the complete regulatory process. We have defined the "regulatory process" to mean any interaction CBER may have with a product from its pre-IND phase throughout its premarket development and subsequently, its postmarketing regulation. On-going training programs targeted for CBER review staff have included Reviewer Training, Case Study Seminars, and specific topic areas regarding new guidance documents.

Recommendation #5 - Redesign forms to improve integrity of BIMS data.

CBER agrees with the recommendation. FDA has established a working group that will meet and discuss possible revisions to the Form FDA 1571. This will be a collaborative effort between the Center for Biologics Evaluation and Research and the Center for Drug Evaluation

and Research. In addition, CBER's Managed Review Committee is evaluating the potential development of a guidance document to advise sponsors on the type of information that needs to be included in the cover letter of an IND so that information will be readily accessible by DCC for subsequent database entry.

Recommendation #6- Consider the legal feasibility of imposing sanctions for sponsors who do not submit annual reports.

CBER does not agree with the recommendation. Given the number of noncompliant facilities, the proposal to impose sanctions would require additional agency resources. Pursuing a civil money penalty case is a very resource intensive activity, and would not be practical for the agency to follow this course of action against any but the most non-compliant entities. Most commercial IND sponsors do not receive significant federal funds. Implementing a system of withholding federal funding of non-compliant entities would prove to be low yield and not worth the cost.

The action of imposing sanctions, other than already existing sanctions, on sponsors who do not submit annual reports may require additional statutory authority along with modification of existing regulations. Current FDA regulations, 21 CFR 312.42, do not provide for the agency to place an IND on clinical hold for failure to file an annual report.

FDA

OM/OHRMS/DMSP

Note

Date: JUN 25 1998

To: Carol Lessans

Subject: Clarification of Agency Response on "Review of The Annual Reporting Process for investigational New Drugs Regulated by FDA's Center for Biologics Evaluation and Research" (A-I 5-96-50001)

As requested, a reevaluation has been made of our response to your report entitled, "Review of the Annual Reporting Process for Investigational New Drugs Regulated by FDA's Center for Biologics Evaluation and Research." The Center has provided clarification to address your concerns and copies of the following documents: 1) 11/12/97 Letter from Dr. Shalala, 2) FDA Modernization Act of 1997, and 3) FD&C Act.

Please review the attached documents which address or relate to your specific concerns. If additional information is needed, we will be glad to facilitate the process.



Paul Jones

Attachment



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

DATE: June 19, 1998

FROM: Director, Office of Communication, Training and Manufacturers Assistance (HFM-40) *[Signature]*

RE: Response to OIG's Concerns Regarding the OIG Draft Report, "Review of The Annual Reporting Process for Investigational New Drugs Regulated by FDA's Center for Biologics Evaluation and Research" (A-15-96-50001)

TO: Division of Management, Service and Policy
Attn: Robin Phipps, HFA-27

This is in responses to the auditors concerns regarding CBER's comments/response to the OIG draft report "Review of The Annual Reporting Process for Investigational New Drugs Regulated by FDA's Center for Biologics Evaluation and Research".

In reference to page 5, CBER's comments were meant to clarify that OTRR's SOP for the collection of annual reports is not officially a Center-wide SOP, although as the auditors correctly noted it is currently used Center-wide. This SOP is used as guidance by the other two review offices pending CBER's development of a Center-wide SOP.

Regarding the issue of PDUFA funding, although the Agency was not technically prohibited from using PDUFA funds for review and oversight of INDs in effect for the period of the OIG IND audit, FDA allocated PDUFA I funds for priorities related to the Performance Goals, i.e. to decrease FDA's review time for licensing (marketing) applications. IND reviews were not addressed in the PDUFA I Performance Goals. The intent of PDUFA I and II is to expedite the review and approval process so that new drugs and biologic products can be introduced to the market at an earlier date. We believe that the Performance Goals reflect the expectations of Congress for expending the PDUFA funds and have directed our resources accordingly. Although not specifically addressed in FDA Modernization Act of 1997 (FDAMA), certain aspects of IND review are part of the Performance Goals of PDUFA II. Performance goals for meetings with manufacturers regarding IND clinical protocol agreements and clinical holds are part of PDUFA II implementation. Attached is a copy of the letter from Secretary Shalala to Senator Jeffords with the enclosed Performance Goals. The Performance Goals and FDAMA are also available on CBER's website at: <http://www.fda.gov/cber/fdama.htm>.

In further response to Recommendation #6, CBER will evaluate existing authorities, resources and mechanisms available to enhance compliance with 21 CFR 3 12.33.

I hope this information is helpful.

Attachments: 11/12/97 Letter from Dr. Shalala to Sen. Jeffords and Performance Goals
FDA Modernization Act of 1997
FD&C Act

cc: HFM-1
HFM-40(c)
HFM-46