Memorandum

Date AUG 2 1995

From June Gibbs Brown
Inspector General

Subject Review of the Food and Drug Administration's Processing of a New Drug Application for Therafectin (A-15-94-00023)

To Philip R. Lee, M.D.
Assistant Secretary for Health

The attached final report presents the results of our review of the Food and Drug Administration's (FDA) processing of a new drug application (NDA) for Therafectin, a drug developed by Greenwich Pharmaceuticals, Inc. (Greenwich) for the treatment of rheumatoid arthritis. The FDA informed Greenwich in September 1993 that its NDA could not be approved because there was not adequate data demonstrating the drug's effectiveness. This review, requested in March 1994 by Congressman John D. Dingell, was prompted by Greenwich's concerns that FDA did not follow applicable administrative procedures.

We found that, in general, FDA properly processed the Therafectin NDA. We noted certain administrative shortcomings, but found no evidence that they affected the approval status of the Therafectin application. In the final analysis, Greenwich was not able to adequately demonstrate--either to FDA or the Arthritis Advisory Committee--that Therafectin was effective for the treatment of rheumatoid arthritis.

However, we found--as did FDA in its own internal evaluation--that certain administrative improvements can be made to further strengthen the NDA review process. Identified areas in need of improvement include: (1) documentation of meetings and discussions; (2) procedures for advisory committee meetings; (3) use of outside consultants; (4) protocol design; and (5) refuse-to-file actions.

The FDA reviewed a draft of this report, and indicated to us that it accurately reflects the events that occurred with the Therafectin application.

If you have any questions regarding the matters discussed in this report, 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-15-94-00023 in all correspondence relating to this report.

Attachment

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S PROCESSING OF A NEW DRUG APPLICATION FOR THERAFECTIN

JUNE GIBBS BROWN
Inspector General

AUGUST 1995
A-15-94-00023

EXECUTIVE SUMMARY

BACKGROUND

The Food and Drug Administration (FDA) is responsible for approving new drugs. In January 1993, Greenwich Pharmaceuticals, Inc. (Greenwich) submitted a new drug application (NDA) for Therafectin, a drug it developed for the treatment of rheumatoid arthritis. In September 1993, FDA informed Greenwich that its NDA could not be approved because there was not adequate data demonstrating the drug's effectiveness. In October 1993, Greenwich brought its concerns to the attention of the Honorable John D. Dingell, then Chairman of the Subcommittee on Oversight and Investigations (Subcommittee), House Committee on Energy and Commerce. Greenwich generally alleged that FDA did not follow procedures in processing its NDA.

OBJECTIVES

The overall objective of our review was to determine whether FDA properly processed Greenwich's NDA for Therafectin in full compliance with applicable administrative procedures. Our specific objectives were to determine if:

(1) the FDA failed to follow certain administrative procedures as contained in three Greenwich allegations submitted to the Subcommittee; and

(2) the FDA needs to improve its NDA administrative processes, in light of the Therafectin matter.

SUMMARY OF FINDINGS

The Office of Inspector General (OIG) found that, in general, FDA properly processed the Therafectin NDA.

Finding 1: FDA generally followed administrative procedures

Our review of three Greenwich allegations revealed that the drug developer's (sponsor) complaints regarding FDA not following certain administrative procedures were partially substantiated; but, overall, FDA properly processed the Therafectin NDA.

- We found no merit to Greenwich's allegation that FDA inexplicably changed its position concerning the data supporting the drug's effectiveness.

- We substantiated Greenwich's allegation that FDA failed to follow administrative procedures for sponsors to meet with FDA to discuss scientific disputes.

- We partially substantiated Greenwich's allegation that FDA's Division of Pilot Drugs (Pilot Drugs) failed to provide a summary assessment that it promised to the sponsor in advance of a January 27, 1994 Arthritis Advisory Committee (advisory committee) meeting. However, the record shows that the agency had previously provided the sponsor copies of the medical and statistical reviews.

These administrative shortcomings do not appear to have affected the approval status of the Therafectin application. In the final analysis, Greenwich was not able to adequately demonstrate--either to FDA or the advisory committee--that Therafectin was effective for the treatment of rheumatoid arthritis.

Finding 2: FDA has an opportunity to improve its NDA administrative processes

Based on our review of the Therafectin NDA, it appears that FDA's overall administrative processes for NDAs are basically sound. We noted that even when there were lapses in the administrative process, FDA provided certain administrative avenues to Greenwich to help discuss differences with the sponsor and to mitigate breaches in communication.

We found that FDA used several administrative techniques to address a contentious situation with Greenwich. Such techniques included using the Office of the Chief Mediator and Ombudsman (Ombudsman); involving top-level Center for Drug Evaluation and Research (CDER) officials to review the scientific and administrative aspects of the NDA; and convening an additional advisory committee meeting to review the Therafectin NDA.

However, we found--as did FDA in its own internal evaluation--that certain administrative policies and procedures can be improved to further strengthen the NDA review process. The FDA has used the Therafectin case, as well as its experience with other NDA reviews, to suggest improvements to the process, with a particular emphasis on developing greater consistency among the various FDA components involved with NDA reviews. Areas where FDA has identified the need to make improvements include the documentation of meetings and discussions; procedures for advisory committee meetings; use of outside consultants; protocol design; and refuse-to-file actions.

SUMMARY

Despite several noted administrative problems, in the final analysis, it appears that FDA, overall, properly processed the Therafectin NDA. The FDA used the Therafectin NDA review case to identify ways it could further strengthen the NDA process.

The FDA was able to critically examine its own performance in handling the Therafectin matter, and it used this particular NDA experience, as well as its experience in handling other NDAs, to identify areas where general improvements could be made.

The FDA reviewed a draft of this report, and indicated to us that it accurately reflects the events that occurred with the Therafectin application.

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INTRODUCTION

BACKGROUND

The FDA is responsible for approving new drugs. In January 1993, Greenwich submitted an NDA for Therafectin, a drug it developed for the treatment of rheumatoid arthritis. In September 1993, FDA informed Greenwich that its NDA could not be approved because there was not adequate data demonstrating the drug's effectiveness.

In October 1993, Greenwich brought its concerns to the attention of the Honorable John D. Dingell, then Chairman of the Subcommittee. Greenwich generally alleged that FDA did not follow procedures in processing its NDA.

New Drug Approval Process

As authorized by law and regulations, FDA approves new drugs before they are marketed based on data that sponsors submit to the agency demonstrating the drug's safety and effectiveness. Early in the drug development process, a sponsor files with FDA an investigational new drug application (IND) to obtain the agency's permission to conduct clinical tests of the drug on human subjects. The FDA generally provides the sponsor its views about the testing methodologies (protocols) to be used during the testing phase (clinical trials).

Once the testing is complete, the sponsor usually submits the results to FDA in an NDA. Within 60 days after FDA receives an NDA, the agency determines whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review. The regulatory review clock provides for FDA review within 180 days of receipt of the application. At the conclusion of the NDA review, FDA sends the sponsor a letter indicating that the application is approved ("approval letter"); a letter stating that the application is basically capable of being approved providing certain issues are resolved ("approvable letter"); or a letter indicating that the application may not be approved ("not approvable letter"). The sponsor may at any time request withdrawal of an application that is not yet approved, without prejudice to any future resubmission, by notifying FDA in writing ("withdrawal letter").

The sponsor's NDA must show that the drug is safe and must include substantial evidence, consisting of adequate and well-controlled clinical studies, demonstrating that the drug is effective for its intended use. In most cases, the sponsor must present data from two replicatable clinical trials showing that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling for the drug product.

The law and regulations specify a hearing process for sponsors who want to appeal FDA's decision that an application cannot be approved. The Director of CDER will provide the aggrieved sponsor with a notice of opportunity for hearing on the agency's proposal to refuse to approve an application. The notice generally states the reasons for the action and the proposed grounds for the order. The FDA will publish the notice in the Federal Register, and state that the sponsor who wishes to participate in a hearing has 30 days after the date of publication of the notice to file a written notice of participation and request for hearing.

FDA's CDER Organization

The CDER is responsible for reviewing and approving new drugs intended for humans. Within CDER, Pilot Drugs handles new drugs classified as narcotics, analgesics, and anesthetics, and drugs developed to treat addictive disorders. Pilot Drugs, formed in 1989 to develop and demonstrate innovative methods to enhance the NDA process, reported directly to CDER's Director until August 1993, when management responsibility was transferred to the Office of Drug Evaluation II (ODE II). The other major drug reviewing office is the Office of Drug Evaluation I (ODE I). Both ODE I and II report directly to CDER's Director. The ODE I and II are both involved in NDA reviews of drugs identified by FDA as new molecular entities, which are drugs whose active ingredients have never before been marketed.

In addition to CDER, other groups may become involved in a new drug review, including:

-- Advisory committees: as part of the review process, FDA often relies on its advisory committees to provide independent expertise and technical assistance, and to provide a forum for public discussion of certain controversial issues. These committees do not make approval decisions; they offer recommendations to FDA.

-- Outside consultants: provide a useful service to FDA in helping the agency meet reviewing demands in areas with heavy workloads or where special expertise can be provided.

Greenwich and Therafectin

The drugs FDA has approved in the past to treat rheumatoid arthritis have been one of two types: (1) Non-steroid anti-inflammatory drugs, which are indicated to alleviate the pain associated with arthritis; or (2) disease modifying anti-rheumatoid drugs, which alter or improve the disease condition. Therafectin was neither of these two types of drugs, and according to Pilot Drugs' reviewers, could not be tested with the protocols used for the above-cited classes of arthritis drugs.

In the early 1980s, Greenwich began to study whether Therafectin was safe and effective in the treatment of rheumatoid arthritis. During this IND testing phase, Greenwich and Pilot Drugs staff interacted through several telephone conference calls and face-to-face meetings. In addition, FDA called on the advisory committee to obtain its views about the sponsor's drug testing results. Therafectin was presented and discussed at two closed sessions of the advisory committee (May 24, 1990 and September 22, 1992) before the NDA was submitted to FDA on January 11, 1993.

Several meetings transpired before Pilot Drugs issued a formal "not approvable letter" to Greenwich on September 10, 1993. The "not approvable letter" cited the lack of substantial evidence of effectiveness as the basis for FDA not approving the NDA for Therafectin. After several meetings with the sponsor, FDA agreed to present the NDA, for the third time, at an open session of the advisory committee on January 27, 1994. The advisory committee voted to recommend that Therafectin not be approved for the treatment of rheumatoid arthritis.

OBJECTIVES, SCOPE, AND METHODOLOGY

Objectives

The overall objective of our review was to determine whether FDA properly processed Greenwich's NDA for Therafectin in full compliance with applicable administrative procedures. Our specific objectives were to determine if:

(1) the FDA failed to follow certain administrative procedures as contained in three Greenwich allegations submitted to the Subcommittee; and

(2) the FDA needs to improve its NDA administrative processes, in light of the Therafectin matter.

Scope

Our review was performed in response to the Honorable John D. Dingell's March 1994 request to OIG to review FDA's Pilot Drugs' handling of the IND and NDA for Therafectin, which covered a time period spanning from November 1986 through May 1994.

Our review was conducted in accordance with generally accepted government auditing standards. It was performed during the period May 1994 through April 1995, at FDA offices located in Rockville, Maryland. We did not independently make a judgment regarding the scientific decisions made by FDA or the advisory committee in regard to the approvability of Therafectin. Our review focused primarily on FDA's interaction with Greenwich during the IND and NDA phase of the drug's development, and the administrative handling of the sponsor's new drug application.

Methodology

We examined pertinent laws, regulations, and policies followed by FDA for NDAs, and attended a briefing on the new drug development process presented by CDER officials. To assess the adequacy of FDA's processing of the Therafectin NDA, we reviewed several of Greenwich's specific allegations regarding the NDA review process. Regarding Greenwich's allegations, we reviewed the firm's and FDA's records of meetings, telephone conversations, and advisory committee meetings.

We also examined FDA re-reviews conducted in April and May 1994, about 5 months after Greenwich presented its concerns to Congress. To augment our review of these documents, we interviewed selected current and former FDA officials who participated in the Therafectin review. In addition, we spoke with the previous Greenwich president, who resigned his position at the end of May 1994, and who made the allegations against FDA.

We reviewed documentation generated by both Greenwich and FDA beginning in 1986, which is the time when the two parties initiated meetings regarding the IND. Our examination of documents extended through the post-NDA phase, which concluded with FDA re-reviews of the Therafectin process, dated May 1994. During our review, we also requested and received in October 1994 an internal evaluation of how FDA drug officials viewed the agency's handling of the Therafectin matter, and ways the NDA process could be improved.

DETAILED FINDINGS

The OIG found that, in general, FDA properly processed the Therafectin NDA. Our review of three Greenwich allegations revealed that the sponsor's complaints regarding FDA not following certain administrative procedures were partially substantiated; but, overall, FDA properly processed the Therafectin NDA. It appears that FDA's overall administrative processes for NDAs are basically sound, but can be strengthened. The FDA plans to make improvements to the NDA administrative process regarding: documentation of meetings and discussions; procedures for advisory committee meetings; use of outside consultants; protocol design; and refuse-to-file actions.

FDA GENERALLY FOLLOWED ADMINISTRATIVE PROCEDURES

Greenwich alleged that FDA: (1) inexplicably changed its position concerning the data supporting the drug's effectiveness; and (2) failed to follow procedures, outlined in 21 Code of Federal Regulations (C.F.R.), section 314.102(c) and (d), allowing for the discussion of scientific disputes and debates between the agency and the sponsor. Greenwich also charged that FDA's Pilot Drugs failed to provide the documentation that it promised to the sponsor in advance of a January 27, 1994 advisory panel meeting, causing the sponsor to be unprepared for the meeting.

Our review of three Greenwich allegations revealed that the sponsor's complaints regarding FDA not following certain administrative procedures were partially substantiated; but, overall, FDA properly processed the Therafectin NDA. Following is a detailed analysis of the three allegations.

Greenwich Allegation 1: The FDA inexplicably changed its position concerning the data supporting the drug's effectiveness

The files and records did not support this allegation made by Greenwich. We found that during the IND development phase, which covered a lengthy time period from 1986 through 1992, FDA informed Greenwich several times of the weaknesses in its clinical trial data supporting the effectiveness of its drug Therafectin.

The record shows that although some positive signals about the clinical evidence of the drug's effectiveness were communicated by Pilot Drugs to Greenwich in 1990, data subsequently became available that caused Pilot Drugs to question the adequacy of the evidence supporting the drug's effectiveness. In addition, the advisory committee, in closed sessions held in May 1990 and September 1992, raised doubts about the drug's effectiveness--doubts that were openly communicated to Greenwich.

Because of the questions regarding Therafectin's testing results, Pilot Drugs, during discussions and meetings held with Greenwich in November and December 1992, strongly discouraged the firm from submitting an NDA. Instead, it recommended that Greenwich perform a unique type of analysis (meta analysis) of its prior studies to shed new light on the issue of the drug's effectiveness. Thus, FDA sent a strong "signal" to the sponsor by suggesting that if the company submitted its NDA without the desired meta analysis, Pilot Drugs would refuse to file the application since it would be considered incomplete.

Despite such discouragement, Greenwich submitted its NDA in January 1993, and later learned from Pilot Drugs during a March 12, 1993 telephone conference call that the application could not be approved from a clinical standpoint. However, the record shows that FDA officially filed the Greenwich NDA on this date. A draft "not approvable letter" was subsequently sent to Greenwich on July 22, 1993. At the same time, FDA sent a draft "withdrawal letter" along with the agency's reports on the results of its review of Therafectin, which was performed by its consultant medical reviewer and its staff statistical reviewer. Pilot Drugs then held meetings with Greenwich in July, August, and September 1993, before it officially issued a "not approvable letter" on September 10, 1993.

In summary, our conclusion echoes FDA's October 1994 internal evaluation, in which the agency concluded that Greenwich had been informed of the weaknesses in Therafectin's clinical data over a significant period of time prior to Pilot Drug's decision to not approve the application.

Greenwich Allegation 2: The FDA failed to follow administrative procedures for sponsors to meet with FDA to discuss scientific disputes

We substantiated the allegation--as did FDA in its internal evaluation--that Pilot Drugs was not fully responsive to Greenwich's request for a meeting on two separate occasions: (1) after the sponsor submitted its NDA; and (2) prior to a January 1994 advisory committee meeting. In our judgement, these meetings would likely not have changed FDA's position on Therafectin, but could have served to mitigate negative feelings on the part of Greenwich.

Greenwich's Request for Meeting During the NDA Process

Regulations in 21 C.F.R., section 314.102(c) and (d) provide the sponsor an opportunity to meet with FDA to discuss deficiencies in the NDA, either 90 days after the agency receives the NDA (90-day conference) or at the end of FDA's review (end of review conference). Our review of the files and records shows that on May 18, 1993, 4 months after it submitted the Therafectin NDA, Greenwich asked to meet with FDA. In its request, Greenwich asked for the meeting to discuss the progress and status of the NDA, but it did not refer specifically to a 90-day conference or meeting.

Despite Greenwich's request, Pilot Drugs did not provide a timely meeting for the sponsor. The record shows no further response by FDA until July 22, 1993, when Pilot Drugs faxed copies of a draft "not approvable letter" and a draft NDA "withdrawal letter", an action that suggested Greenwich make a choice between the two options. Also submitted to Greenwich at this time were the FDA reports on the results of the agency reviews of Therafectin performed by its consultant medical reviewer and its resident statistical reviewer. These two reports were the basis for the position taken by FDA that the Therafectin application could not be approved.

In its October 1994 internal evaluation of the Therafectin review process, FDA concluded that Pilot Drugs should have been more responsive to Greenwich's request for a meeting during the NDA review period. We, too, believe a meeting should have been held during this period, even if Pilot Drugs only reiterated its previous observations that testing data did not support Therafectin's effectiveness. If Pilot Drugs had used such a meeting to attempt to convince Greenwich of the NDA deficiencies, it is possible that the ensuing friction between Greenwich and various components of FDA would not have occurred. This lack of communication between Greenwich and Pilot Drugs led the sponsor to continue to seek further FDA responses to its NDA application, which are described below.

Greenwich's Request for a Meeting Prior to the January 1994 Advisory Committee Meeting

In a second case, prior to the January 1994 advisory committee meeting, Greenwich received a requested meeting with FDA, but the meeting was not held in a timely manner.

After Pilot Drugs issued the official "not approvable letter" to Greenwich in September 1993, an agreement was subsequently made between Greenwich and FDA that the advisory committee would review the Therafectin NDA. It is important to note that the scheduling of this advisory committee--the third for the Therafectin NDA--was an unusual undertaking for FDA because the agency normally does not convene an advisory committee when no new data are presented.

Greenwich called Pilot Drugs on October 20, 1993, to request a meeting to discuss the advisory committee meeting scheduled for the last week of January 1994. The meeting request was reiterated in a Greenwich letter to Pilot Drugs on November 23, 1993, and in a letter from Greenwich's legal counsel to the director of ODE II, CDER, on December 3, 1993. After further discussions with FDA officials, a meeting was scheduled for December 15, 1993, to discuss the clinical trial data and specific issues to be presented to the advisory committee in January 1994. Thus, even though the meeting was eventually held, it was more than 3 months since FDA officially issued the "not approvable letter" to Greenwich.

In its October 1994 internal evaluation of the Therafectin review process, FDA concluded that Pilot Drugs appeared to have been unnecessarily reluctant to meet with Greenwich in the period prior to the January 27, 1994 advisory committee meeting. Our findings support FDA's observations in this matter. We agree that Pilot Drugs should have been more responsive to Greenwich's request for a meeting during this period, even if it only reiterated its previous findings that testing data did not support Therafectin's effectiveness.

Greenwich Allegation 3: Pilot Drugs failed to provide a summary assessment that it promised to the sponsor in advance of a January 27, 1994 advisory committee meeting, causing the sponsor to be unprepared for the meeting

We partially substantiated Greenwich's allegation that, because FDA did not provide a summary assessment of Therafectin, the sponsor was then unprepared for an advisory committee meeting. Our review of the records and files related to the January 1994 advisory committee revealed that, although not required to do so, FDA should have provided Greenwich with a summary assessment of the Therafectin NDA prior to the advisory committee meeting. However, we do not agree that Greenwich was unprepared for the meeting, because FDA had sent the firm copies of the medical and statistical reviews several months before the meeting, in July 1993.

The record shows that, during a December 1993 meeting, Greenwich requested--and FDA agreed to provide--a unified summary of FDA's comments on the specific Therafectin studies included in the NDA and the agency's basis for not approving the application. Greenwich requested this summary because its management felt frustrated by what appeared to be conflicting statements in various documents that FDA had previously sent to the sponsor regarding the Therafectin studies. We determined that Pilot Drugs and upper-level CDER management attempted to develop a unified summary prior to the advisory committee meeting, but were not able to successfully prepare it due to time constraints and the complexity of the issues involved. According to the October 1994 FDA internal evaluation of the Therafectin matter, FDA provided copies of the medical and statistical reviews to Greenwich and the advisory committee members in advance of the January 27, 1994 meeting.

Although we identified no administrative requirement for FDA to provide a sponsor with such a summary, we believe that the agency should have acted on its verbal promise. More importantly, it appears that FDA, recognizing that Therafectin was a contentious matter, missed a significant opportunity to clearly communicate its written views to both the sponsor and the advisory committee. If such a written summary had been prepared, it could have helped both Greenwich and the advisory committee focus their discussion during the meeting.

FDA HAS AN OPPORTUNITY TO IMPROVE ITS NDA ADMINISTRATIVE PROCESSES

Based on our review of the Therafectin NDA, it appears that FDA's overall administrative processes for NDAs are sound. However, we found--as did FDA in its own internal evaluation--that certain administrative policies and procedures can be improved to further strengthen the NDA review process.

Administrative Opportunities FDA Afforded to Greenwich

We noted that even when there were lapses in the administrative process, as described above, FDA provided certain administrative avenues to Greenwich to help resolve differences with the sponsor and to mitigate breaches in communication.

The record shows that FDA used several administrative techniques to address a contentious situation with Greenwich. Such techniques included using the agency's Ombudsman to help resolve conflicts which arose during the NDA review phase; involving top-level CDER officials to review the scientific and administrative aspects of the NDA; and convening an additional advisory committee panel meeting to review the Therafectin NDA.

CDER Efforts to Improve the NDA Process

At the request of the OIG, CDER management provided an extensive analysis of Greenwich's criticisms of FDA's conduct of the Therafectin review. Some of the criticisms were not well-founded; however, FDA identified several procedural deficiencies in the NDA review process. Through CDER's internal evaluation of the Therafectin matter, and its assessment of CDER-wide operations, FDA management has determined that certain administrative policies and procedures can be improved to further strengthen the overall NDA process.

The CDER has identified numerous actions which we believe can help avoid future contentious relationships with new drug sponsors. The actions being implemented or planned include: (1) improving the documentation of meetings and discussions between drug sponsors and agency staff; (2) increasing the effectiveness of advisory committee meetings by scheduling them for maximum benefit to the sponsor, and providing committee members with adequate information about the drug prior to the meeting; (3) ensuring that outside consultants have frequent communications with FDA staff involved with the drug being reviewed; (4) ensuring that FDA and sponsors carefully consider their study designs so that they are consistent with study objectives; and (5) providing additional guidance and monitoring of refuse-to-file actions by CDER components involved in the new drug application review process.

SUMMARY

The OIG review of the Therafectin regulatory review process showed that, despite certain noted administrative problems, FDA appeared to have properly processed Greenwich's NDA. However, we believe, as does the FDA, that the agency could have better handled certain administrative aspects of the process.

The FDA was able to critically examine its own performance in handling the Therafectin matter, and it used this particular NDA experience, as well as its experience handling other NDAs, to identify areas where general improvements could be made.

The FDA reviewed a draft of this report, and indicated to us that it accurately reflects the events that occurred with the Therafectin application.

If you have any questions regarding the matters discussed in this report, please call me or have your staff contact Joseph J. Green, Assistant Inspector General for Public Health Service Audits, at (301) 443-3582.