DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Memorandum

Date SEP 16 1992

From Bryan B. Mitchell
Principal Deputy Inspector General

Subject Follow-Up Review of the Food and Drug Administration's Generic Drug Approval Process (A-15-91-00025)

To James 0. Mason, M.D., Dr. P.H.
Assistant Secretary for Health

The attached final report presents the results of our follow-up review of the Food and Drug Administration's (FDA) progress in implementing recommendations contained in our management advisory report entitled, "Vulnerabilities in the Food and Drug Administration's Generic Drug Approval Process" (A-15-89-00051), issued on August 17, 1989. For the past 3 years, the Secretary of Health and Human Services has reported the absence of adequate internal controls in FDA's generic drug approval process as a material weakness to the President and Congress under the provisions of the Federal Managers' Financial Integrity Act of 1982.

The Office of Management and Budget (OMB), from 1989 through 1991, designated the application review process for generic drug approval as a high-risk area, highlighting the need for the agency head to personally ensure that corrective action is taken. On December 17, 1991, the Commissioner of Food and Drugs made a number of commitments to OMB for corrective actions to address the above issues. In the President's Fiscal Year 1993 budget, OMB deleted the generic drug application review process from the high-risk list, concluding that "all major corrections have been completed."

Our follow-up review disclosed that FDA has not taken sufficient action to correct this material weakness. We determined that FDA needs to: (1) modify the method by which generic drug applications are assigned to reviewers to remove any opportunity for showing partiality or favoritism: (2) revise its "first-in, first-reviewed" policy for generic drugs because the current policy may allow for the unequal treatment of drug firms' applications; (3) develop comprehensive guidelines to assure that generic drug applications are reviewed in a uniform and consistent manner: and (4) establish a quality control review system outside the Office of Generic Drugs to ensure the propriety of individual generic drug application reviews and the integrity of the review process.

The Public Health Service (PHS), in its July 24, 1992 response to our draft report, concurred with our recommendations. However, full implementation of actions underway and planned is not expected to be completed until some future date. Consequently, this issue should continue to be reported as a material internal control weakness, The PHS comments have been incorporated into the Agency Comments and Office of Inspector General Response section of the report and are included in their entirety in the Appendix.

We would appreciate your comments on this final report within 60 days. Should you wish to discuss the issues raised by our review and recommendations, please call me or have your staff contact Daniel W. Blades, Assistant Inspector General for Public Health Service Audits, at (301)443-3583.

Attachment

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

FOLLOW-UP REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S GENERIC DRUG APPROVAL PROCESS

SEPTEMBER 1992 A-15-91-00025

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This final report provides the results of our follow-up review of the Food and Drug Administration's (FDA) progress in implementing recommendations contained in our management advisory report entitled, "Vulnerabilities in the Food and Drug Administration's Generic Drug Approval Process" (A-15-89-00051), issued on August 17, 1989. That report was requested by the then Commissioner of Food and Drugs (Commissioner) and the Chairman of the House Subcommittee on Oversight and Investigations (Subcommittee), Committee on Energy and Commerce, after disclosures were made of fraud and corruption within the generic drug application review process. The report showed that a material internal control weakness existed in the way generic drug applications were reviewed and approved by FDA, which allowed preferential treatment to be given to certain drug firms.

Specifically, the August 1989 report stated that FDA: (1) arbitrarily assigned and reassigned generic drug applications to review chemists (reviewers); (2) lacked adequate guidelines to ensure the consistent review of applications; and (3) needed a quality control review system to ensure that applications are properly reviewed and that all generic drug firms receive equitable treatment.

From 1989 through 1991, the Secretary of Health and Human Services (HHS) reported the absence of adequate internal controls in FDA's generic drug approval process as a material weakness to the President and Congress under the provisions of the Federal Managers' Financial Integrity Act of 1982 (FMFIA). In addition, the Office of Management and Budget (OMB), from 1989 through 1991, designated the application review process for generic drug approval as a high-risk area, highlighting the need for the agency head to personally ensure that corrective action is taken.

This follow-up review disclosed that FDA has not taken sufficient action to correct this material weakness. Although FDA has implemented a system for the assignment of Abbreviated New Drug Applications (ANDA)[1] to the various review branches based on the pharmacological class of the drug, this system still allows branch chiefs to subjectively assign ANDAs to fast or slow reviewers or to reviewers with large or small backlogs. The branch chief's assignment decision can influence the order in which ANDAs are approved and may result in preferential treatment for certain drug firms. In addition, ANDAs are reviewed in the order they appear in a reviewer's queue rather than the date they are received in the review branch. Since reviewers' backlogs may vary significantly among reviewers, FDA's "first-in, first-reviewed" policy will not ensure review of applications in order of receipt.

Also, few FDA guidelines have been developed since July 1989 to provide specific guidance to reviewers to ensure consistency in the review process. Finally, FDA has not implemented a quality control system to ensure the propriety of ANDA reviews and the integrity of the overall ANDA review process.

Although OMB recently removed the application review process for generic drug approval from its high-risk list, the material internal control weaknesses of the process have not been resolved and should continue to be reported by the Secretary of HHS under the provisions of the FMFIA.

BACKGROUND

In June 1988, the Subcommittee received allegations of improprieties associated with the generic drug application review process at FDA. Specifically, it was alleged that certain employees in FDA's then Division of Generic Drugs willfully manipulated the application review process to give preferential treatment to certain pharmaceutical companies. The Subcommittee referred criminal allegations to the Office of Inspector General (OIG) for investigation. The OIG investigation into these allegations, under the auspices of the United States Attorney's Office, also identified fraud and misrepresentation in the generic drug approval process, including false statements and claims, as well as product substitution. As of July 1992, 29 individuals, including 5

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[1] In order to receive approval to market a generic drug, a firm must submit an ANDA to FDA. An ANDA contains, among other data, information on the generic drug's therapeutic equivalence to the brand name drug, the generic drug's chemistry, and samples of proposed labeling.

FDA employees, and 8 companies have pleaded guilty or have been found guilty of fraud or corruption charges. The investigation is continuing.

The Office of Generic Drugs (OGD), located in FDA's Center for Drug Evaluation and Research (CDER) in Rockville, Maryland, reviews original ANDAs, their amendments and supplements, and determines their approvability based on medical and scientific data. The ANDAs undergo three separate reviews: (1) bio-equivalence, which determines if the generic drug is thera-peutically equivalent to the brand name drug; (2) labeling, which assesses the adequacy of the generic drug label: and (3) chemistry, which evaluates the methods used to manufacture the drug.

The OIG's August 1989 audit and this follow-up audit of the generic drug application review process primarily focused on the chemistry review because the OGD employee responsible for this review--the chemistry reviewer--summarizes the information from all three reviews and recommends whether the ANDA should be approved.

The OGD comprises six ANDA chemistry review branches, an antibiotic drug review branch, three bioequivalency review branches, a labeling review staff, a program support staff, and a management staff. The FDA field personnel provide support to OGD by conducting manufacturing plant inspections, product testing, and product monitoring. During Fiscal Year (FY) 1991, OGD received 1,453 original and amended generic drug applications and approved 141. For FY 1992, FDA expects to spend about $33 million for generic drug evaluations.

OBJECTIVE, SCOPE AND METHODOLOGY

The objective of our review was to determine FDA's progress in implementing recommendations made in the OIG's management advisory report entitled, "Vulnerabilities in the Food and Drug Administration's Generic Drug Approval Process,'* issued on August 17, 1989. We verified, to the extent possible, the actions that FDA stated were taken or proposed in its November 6, 1989 response to the OIG report.

We reviewed all policy and procedural guides issued by FDA's OGD relating to the ANDA review process. We interviewed OGD officials, reviewed pertinent documents to obtain information on the method for assigning and reassigning ANDAs to reviewers, and selected a judgmental sample of ANDA files and related computer-generated reports to examine the assignment and review process. We also obtained information on the quality control system for evaluating the propriety of these reviews and assessing the integrity of the generic drug application review process. Further, we reviewed FDA's

interim rule for the collection and testing of bioequivalency samples submitted by ANDA applicants to demonstrate that their generic drugs are therapeutically equivalent to the brand name drugs. In addition, we reviewed a consultant team's report,[2] which discussed several weaknesses in the generic drug application review process.

A draft copy of our proposed report was submitted to the Public Health Service (PHS) on May 11, 1992, for the purpose of providing PHS an opportunity to review and comment on the results of our follow-up review. The PHS comments pertaining to our recommendations, dated July 24, 1992, have been incorporated into the Agency Comments and OIG Response section of this report and are included in their entirety in the Appendix.

Our review, performed from April 1, 1991 to September 30, 1991 at the OGD offices in Rockville, Maryland, was conducted in accordance with generally accepted government auditing standards.

RESULTS OF FOLLOW-UP REVIEW

Our follow-up review disclosed that FDA has not taken sufficient action to implement all of the recommendations made in our August 1989 report to correct the weaknesses in the generic drug application review process. Our evaluation of FDA's implementation of each of our recommendations is presented below.

ASSIGNMENT OF GENERIC DRUG APPLICATIONS

OIG Recommendation: Develop policies and procedures for *the* random assignment of ANDAs to reviewing chemists, or for other appropriate methods for reducing the opportunity to show any partiality to applicants.

FDA Corrective Action: In response to the OIG's August 1989 report, FDA stated that ANDAs are currently assigned in the following manner. The consumer safety officer delivers the ANDA to the ANDA review branch which handles the particular drug's pharmacological class. The chemistry branch chief then assigns the ANDA to a reviewer, considering the reviewer's expertise with the drug and ANDA backlog.

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[2] "Fairness in the Food and Drug Administration's Generic Drug Program: An Independent Consultant Review of Charges of Unfairness and Retaliation": Arthur H. Kibbe, Ph.D., James A. Kopf, and John E. Zarembo, Ph.D., April 1991.

The FDA also stated that if generic drug applications for the same drug product came in simultaneously from several drug firms, those applications would be consciously assigned to different reviewers so that their reviews would proceed independently.

OIG Follow UP: We determined that OGD's method for assigning ANDAs to reviewers is basically the same as that used prior to the generic drug investigation, which allowed partiality to certain drug firms. The ANDAs are assigned to review branches based on the pharmacological class of the drug and then subjectively assigned by the branch chief to individual reviewers. The subjective assignment of ANDAs by the branch chief to reviewers still allows the potential for partiality to be shown to certain drug firms.

In our August 1989 report, we noted instances where applications for the same drug product that were submitted to FDA by competing companies at the same time were assigned to the same reviewer. We noted that this situation would allow the reviewer to control these applications and be in a position to influence their order of approval. For example, the reviewer could ensure that a particular firm knew about deficiencies in its applications before the competing firms were aware of their deficiencies, or the reviewer may have performed a superficial review of one firm's application while performing comprehensive reviews of the other firm's applications.

Despite OGD's policy requiring that ANDAs for the same drug that are received simultaneously be assigned to different reviewers, we were able to identify a situation where this policy was not followed. During our follow-up review, we noted, for example, that ANDAs for the same drug product, ketoprofen, submitted by five competing firms, were received in OGD on the same day. The OGD branch chief did not follow FDA's stated policy in this area and assigned these ANDAs to the same reviewer.

We also determined that OGD branch chiefs are not following OGD policy to consider a chemist's backlog when assigning ANDAs. In analyzing the reviewers' workload for a l-month period during May 1991, we noted that ANDA backlogs ranged from 5 to 53. As discussed below, backlogs can affect the sequence of application reviews.

The OGD needs to modify its current assignment system to remove a branch chief's subjectivity when assigning ANDAs and to equalize reviewer workloads. One way that this can be done is for the branch chief to hold the ANDA and then assign it to the next available reviewer. This process should contribute toward two goals: (1) reviewing ANDA's in the order in which

they are received in the review branch; and (2) alleviating workload imbalances.

OIG Recommendation: Ensure that exceptions to the "first-in, first-reviewed" policy *are* uniformly applied by all chemists, and ensure that reasons for reviewing and approving an **ANDA** out of sequence from the order it was received are properly documented in the **ANDA** file.

FDA Corrective Action: According to OGD, **"first-in, first-reviewed"** pertains to the order of review of **ANDAs** by individual reviewers, not the order in which **ANDAs** are received in the review branch. Through its monitoring system, OGD ensures that **ANDAs** are reviewed in the order that they appear in a reviewer's queue. If an **ANDA** is reviewed out of sequence, the reasons are documented in the **ANDA** file.

OIG Follow up: The **OGD's** interpretation of the "first-in, **first-reviewed"** policy--that **ANDAs** should be reviewed in the order that they appear in a reviewer's queue, not the order that they are received in the review branch--is unfair to drug firms. This is because one firm's **ANDA,** submitted to FDA before another firm's **ANDA,** may be reviewed later since it may be assigned to a reviewer with a large backlog. The table below shows some examples where drug **firms' ANDAs** will be reviewed after other drug **firms' ANDAs** even though they were received earlier.

EXAMPLES OF ORIGINAL **ANDAS** RECEIVED AND REVIEWED BY OGD **MAY** 1991

ANDA	Firm	Date **ANDA** Received	Not Approvable Letter Issued[3]	Elapsed Reviewing Days	Chemist
20417	A	09/11/89	Pending	599	1
20522	B	11/02/89	Pending	547	2
20501	C	01/30/90	Pending	458	3
32540	D	04/04/90	Pending	394	4
20552	E	04/20/90	Pending	378	5
20622	F	08/02/90	01/31/91	182	6
20643	G	10/01/90	03/08/91	158	7
31320	H	10/04/90	05/09/91	217	3
31321	I	10/25/90	05/21/91	208	8
31325	H	11/06/90	04/24/91	169	1

NOTE: Not actual **ANDA** numbers

[3] **A** not approvable letter is a letter FDA issues to a drug firm describing which areas in the **ANDA** are deficient and why. A not approvable letter, issued for virtually all **ANDAs,** is one of the first actions in the **ANDA** review process.

The examples in this table show that OGD completed its initial reviews of five ANDAs that were received between August 2, 1990 and November 6, 1990, while five ANDAs that were received much earlier--between September 11, 1989 and April 20, 1990--were still pending review. Although we did not sample all original ANDAs to determine the extent of this situation, we believe it is unfair to the drug industry when original ANDAs are not reviewed in the order in which they are received by the review branch.

The following tables show another way in which OGD's interpretation of the "first-in, first-reviewed" policy may be unfair to drug firms. These tables provide examples of how the reviewers' backlogs can influence the sequencing of ANDA reviews.

EXAMPLES OF ANDA PLACEMENT IN A REVIEWER'S QUEUE

ANDA	Firm	Date Received	Place in Reviewer's Queue	Reviewing Chemist
21506	F	09/06/90	10	3
38847	F	09/06/90	40	6
22559	G	09/06/90	23	7
31000	H	09/06/90	11	8
20641	A	02/05/91	23	1
21025	B	02/05/91	21	2
31084	C	02/05/91	28	3
38904	D	02/05/91	15	4
21029	E	02/05/91	51	5

NOTE: Not actual ANDA numbers

Based on their place in the reviewers' queues, ANDAs for certain firms may be reviewed by OGD before or after other firms' ANDAs, even though they were all received on the same day. Continuation of the current OGD "first-in, first-reviewed" policy, coupled with the subjective assignment of ANDAs to reviewers by branch chiefs, may allow for preferential or detrimental treatment for certain drug firms.

OIG Recommendation: Require each request for ANDA reassignment to another chemist, after the initial assignment, be approved and justification included in the ANDA file.

FDA Corrective Action: During our follow-up, OGD officials informed us that when there is a need for reassignment of an ANDA (most often when a reviewer leaves a branch), the branch chief initiates a newly established application reassignment authorization form, which identifies the: (1) ANDA number, drug name, and firm; (2) names of reviewers that the ANDA was

reassigned from and to: (3) date of reassignment; and (4) reason for transfer. An OGD manager must concur with the reassignment. The completed application reassignment authorization form then becomes part of the ANDA file.

OIG Follow up: The OGD has implemented this recommendation. By selecting a judgmental sample, we confirmed that OGD is completing the application reassignment authorization form and placing this form in the appropriate ANDA file.

POLICIES AND PROCEDURES FOR REVIEWING GENERIC DRUG APPLICATIONS

OIG Recommendation: Develop policies and procedures for use by supervisory and review chemists to ensure the consistent and comprehensive review of applications.

FDA Corrective Action: In response to our August 1989 report, FDA stated that it developed 30 policy and procedural guides since July 1989 that it believes will standardize the process by which generic drug applications are reviewed and approved.

OIG Follow UD: This recommendation has not been implemented. In our August 1989 report, we stated that FDA had established few standard operating procedure's for chemists to use and, therefore, was unable to assure that ANDAs would be reviewed in a comprehensive and consistent manner. We stated that the lack of procedures may indirectly favor one company's application for which a reviewer may do a minimal review and adversely effect another company's applications for which a chemist may do an exhaustive review.

We noted that many of the policy and procedural guides developed by FDA have little relevance to the scientific review of ANDAs. For example, guide 1-89 deals with correspondence practices; guide 3-89 deals with handling telephone inquiries; and guide 9-89 deals with providing copies of action documents to messengers and other representatives of ANDA applicants. In addition, guide 10-89 covers meetings with pharmaceutical firm employees or their representatives: guide 11-89 deals with the shredding of carbons and draft reviews and letters: guide 12-89 discusses the number of manufacturing sites permitted in an ANDA; and guide 25-90 deals with the removal of work-related materials from OGD at the end of employment.

We could not identify any internal guides that specifically describe the proper way to perform a substantive review of an ANDA. We noted that on September 11, 1990, an ANDA review branch chief developed a check list of points to be covered during the chemistry review of an ANDA. We believe this is a good starting point for the development of more comprehensive

guidelines for reviewers to use to ensure the thorough review of an ANDA, particularly those sections that deal with the synthesis of the drug substance, raw material controls, manufacturing and processing, laboratory controls, and stability.

The lack of standard operating procedures for the review of ANDAs was also discussed in a consultant group's report entitled, "Fairness in the Food and Drug Administration's Generic Drugs Program," issued in April 1991. The consultants disclosed that:

-- incomplete initial reviews of ANDA submissions by reviewing chemists are the rule rather than the exception:

-- the FDA did not [in 1989], nor does it today, have a set of standards for its review chemists comparable to the standards the FDA requires of the industry:

-- because the reviewers have no division-wide standards, what is important to one may be trivial to another; and

-- there is considerable disparity among the reviewers, especially in regard to specifications, test methods, and other physical measurements.

Given that FDA has failed to develop standard operating procedures to ensure the uniform and comprehensive review of ANDAs, it may be advisable for FDA to allocate a portion of its generic drug resources for the specific development of such procedures.

OIG Recommendation: Supplement the May 10, 1989 memorandum regarding exceptions to the "first-in, first-reviewed" policy by defining and providing examples of minor chemistry deficiencies and including the supplement in the division's operating procedures manual.

FDA Corrective Action: During our follow-up, OGD officials stated that on July 11, 1991, the Director of OGD issued a memorandum entitled, "Modification of Office's Policy Regarding Exceptions to the 'First-in, First-Review&d' Policy." This memorandum defined a minor amendment as follows:

'An amendment is a drug firm's response to a not approvable letter issued by FDA describing deficiencies in the drug firm's application.

> "An amendment may be classified as 'minor' when an experienced review chemist can reasonably be expected to take less than one hour to complete the review (excluding time required to retrieve the application, and to prepare the chemist review documentation and action letter). The presence of a labeling deficiency will not influence the determination: that is, the amendment category will be determined by chemistry issues alone."

The reviewer makes the initial determination as to whether an amendment should be classified as minor. The reviewer's supervisor must then concur with this decision.

OIG Follow up: The OGD has implemented this recommendation by defining a minor chemistry deficiency and including it in OGD's policy and procedures manual.

QUALITY CONTROL REVIEW SYSTEM FOR GENERIC DRUGS

OIG Recommendation: Establish a quality control review system which includes uniform standards for the review of generic drug applications and operating guidelines *for* the generic drug application review process.

FDA Corrective Action: In response to our August 1989 report, FDA stated that it had designated an official in OGD to act as a quality control review officer, whose duties include quality control of all chemistry reviews and proposed approval actions. According to FDA, the quality control review official is to be aided by the policies and procedures established for reviewing generic drug applications.

OIG Follow up: We determined that the quality control review official is part of the OGD management team and reports to the Director of OGD. As such, this arrangement will not necessarily ensure the required objectivity to evaluate individual ANDA reviews or the propriety of the overall ANDA review process. Further, as stated above, OGD does not have policies and procedures to be used for conducting an objective review.

In our August 1989 report, we stated that FDA lacks a quality control system that assures the fundamental integrity and fairness of the ANDA review process. We emphasized that a well designed and properly implemented quality control system should provide all levels of management with the assurance that they are doing their job properly, timely, consistently, fairly, legally, and efficiently. The FDA has not gone far enough in implementing our recommendation to establish a quality control review system because there continues to be an

absence of an independent, objective system to ensure the quality and integrity of individual application reviews and the overall application review process.

In light of the problems that have plagued the generic drug application review process, it is incumbent upon FDA to develop a quality control review system for generic drugs--one that is independent from OGD management and one that is based on a comprehensive set of standard operating procedures for reviewing applications.

OTHER RECOMMENDATIONS MADE IN OUR AUGUST 1989 GENERIC DRUG REPORT

OIG Recommendation: Require branch chiefs to monitor and report to the division director on the progress of ANDA reviews.

FDA Corrective Action: In responding to the OIG's August 1989 report, FDA stated that branch chiefs and division directors now monitor the progress of ANDA reviews by comparing the date of receipt of an ANDA to the date that an action letter[1] for that ANDA was issued. This comparison is done to determine whether ANDAs are being reviewed in a timely manner, and that older ANDAs in a chemist's review queue are reviewed before newer ANDAs in that chemist's queue.

In addition, OGD reported that it has developed a system to improve documentation and tracking of ANDAs recommended for approval. Tracking forms have been developed for this purpose. The OGD managers stated that they meet with the OGD Director twice a month to discuss the status and progress of each ANDA recommended for approval by the chemist.

OIG Follow UD: We confirmed that OGD has implemented a manual process to monitor the progress of individual ANDA reviews and that the OGD Director is apprised of such progress.

The issue of monitoring ANDA reviews was also discussed in an OIG report entitled, "Review of the Food and Drug Administration's Generic Drug Management Information System," issued on July 6, 1990 (A-15-89-00063). In that report, we disclosed that FDA does not produce reports to effectively monitor day-to-day generic drug application review operations or to detect indications of possible manipulation of the review and approval process. We recommended ways in which the generic drug management information system (MIS) could be

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[1] 'Action letters are approval or not approvable letters issued to drug firms by FDA upon completion of the review of the firms' generic drug application.

improved to strengthen management oversight. We are currently conducting a follow-up review of the generic drug MIS to assess FDA's progress in implementing our recommendations.

OIG Recommendation: Require drug firms to submit **bioequivalency samples with the ANDA and validate the authenticity of the samples submitted.**

FDA Corrective Action: In response to our August 1989 report, FDA stated that it was drafting a regulation requiring bioequivalency testing firms to retain reserve samples that can be tested later if questions arise about a drug's bioequivalence.[6]

OIG Follow up: We determined that on November 8, 1990, FDA issued an interim rule in the Federal Reaister requiring manufacturers who conduct in-house bioequivalence tests, and laboratories that conduct such tests under contract for the manufacturer, to retain for 5 years reserve samples of the drug products used in these tests. An FDA field investigator is required to collect the reserve samples during a preapproval inspection of the manufacturer's facilities and of any contract laboratory. The samples are then to be tested in an FDA laboratory. According to FDA, these actions are intended to help it ensure'bioequivalence between generic drugs and their brand-name counterparts, and to help it investigate more fully instances of possible fraud in bioequivalency testing.

OIG Recommendation: Disclose in reports **required by the FMFIA that there is a material weakness in** *the* **internal control** structure *for* **the generic drug approval** process **that allowed preferential treatment to drug firms, and monitor** corrective action until the **weakness is resolved.**

FDA Corrective Action: The Secretary of HHS, since 1989, has reported the absence of internal controls in FDA's generic drug approval process as a material weakness to the President and Congress under the provisions of the FMFIA.

OIG Follow up: The Secretary of HHS has again reported the absence of internal controls in FDA's generic drug approval process as a material weakness in the HHS' FMFIA report for 1991.

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[6]The manufacturer of a generic drug product must demonstrate bioequivalence through studies in humans showing that its product's rate and extent of absorption do not differ from those of the brand name product that was initially approved by FDA.

As part of the FMFIA process, OMB in 1989 designated the application review process for generic drug approval as a high-risk area--an area where the Government's vulnerability is such that an agency head must personally see to its correction as a matter of priority. Subsequent to the high-risk designation, HHS was required to apprise OMB of FDA's progress in implementing corrective actions in the generic drug application review process, including actions delineated in the 1989 OIG report.

In September 1991, we met with FDA officials to discuss the possible removal of the generic drug application review process from OMB's high-risk list and to disclose our findings from our follow-up review of the process. We informed the officials that corrective actions pertaining to the generic drug application review process were not fully implemented. The FDA officials acknowledged that additional corrective actions were needed to address internal control weaknesses in the review process.

On December 17, 1991, the Commissioner made a written commitment to OMB to complete the following activities by December 31, 1991: (1) finalize new policies for the assignment of generic drug applications; (2) finalize a reference document that identifies all policies and procedures to facilitate the chemistry review of abbreviated new drug applications: and (3) assess the concept and feasibility of a quality control review system for generic drug application reviews that would be conducted in conjunction with the proposed quality control pilot program for pioneer drugs currently under development in CDER.

In the President's FY 1993 budget, OMB deleted the application review process for generic drug approval from the high-risk list, concluding that "all major corrections have been completed.@' Despite this action, we believe that failure to meet the commitments made by the Commissioner may result in the generic drug application review process being returned to the high-risk area. The PHS, in its July 24, 1992 response to our draft report, stated that the commitments made by the Commissioner to OMB have been fulfilled.

CONCLUSIONS

The same conditions that enabled the manipulation of the generic drug review process in the late 1980s continued to exist at the time of our follow-up review. This is because FDA has not fully implemented the recommendations made by OIG in its August 1989 report.

Accordingly, we believe FDA should modify the method by which ANDAs are assigned by branch chiefs to reviewers in order to remove any opportunity for showing partiality or favoritism. Such partiality can be shown by assigning ANDAs to a fast reviewer over a slow reviewer, or assigning ANDAs to a reviewer with a small backlog rather than to a reviewer with a large backlog. Also, branch chiefs should not assign ANDAs for the same drug product from competing companies that are simultaneously received in FDA to the same reviewer. Such ANDAs should be independently and concurrently reviewed. The FDA should also revise its "first-in, first-reviewed" policy for generic drugs, which may favor or penalize a drug firm depending on a reviewer's backlog.

We reiterate the need for FDA to develop specific policy and procedural guides for reviewers so that all ANDAs will be comprehensively reviewed in a uniform manner. In addition, an independent quality control system should be established to assess the propriety of individual ANDA reviews and to ensure the integrity of the ANDA review process.

We believe that the Secretary of HHS should continue to report the absence of internal controls in FDA's generic drug approval process as a material weakness under the provisions of the FMFIA. In addition, although OMB has deleted the generic drug application review process from the high-risk list, failure to meet the commitments made by the Commissioner may result in the review process being returned to the high-risk area.

RECOMMENDATIONS

We recommend that you direct the FDA Commissioner to:

-- modify the ANDA assignment method to remove the opportunity for branch chiefs to subjectively assign ANDAs to reviewers:

-- revise the "first-in, first-reviewed" policy to ensure that ANDAs that are received in the review branch first are reviewed first:

-- develop specific written guidelines for reviewing chemists on the proper way for an ANDA to be reviewed:

-- establish a quality control review system outside of OGD to ensure the propriety of individual ANDA reviews and the integrity of the ANDA review process; and

-- continue to report the absence of adequate internal controls in the generic drug approval process as a

material weakness under FMFIA until such time as all recommended improvements have been fully implemented.

AGENCY COMMENTS AND OIG RESPONSE

The PHS, in its July 24, 1992 memorandum commenting on our draft report, concurred with our recommendations. However, full implementation of actions underway and planned is not expected to be completed until some future date. Consequently, this issue should continue to be reported as a material internal control weakness. Its complete response is included in its entirety in the Appendix to this report and certain responses are paraphrased in this section.

The PHS concurred with our recommendation to modify the ANDA assignment method to remove the opportunity for branch chiefs to subjectively assign ANDA's to reviewers. According to PHS, in a memorandum dated December 30, 1991, the Director, OGD, initiated a series of steps which resulted in the full implementation, on June 8, 1992, of a new policy that effectively removes any subjectivity in the assignment of ANDAs. The PHS believes that as a result of OGD's new random assignment system, OIG's concerns regarding reviewer backlog and assignment of applications are no longer relevant.

The PHS comments indicated that OGD has made progress in decreasing the range of application backlogs among reviewers. Our audit cited examples of backlogs of applications ranging from 5 to 53 for different reviewers. However, a May 1992 OGD review of pending applications among reviewers indicated that the widest range of backlogs of applications ranged from 2 to 14 for 1 branch. We are encouraged by the reported decrease in the range of application backlogs among reviewers and believe that the random assignment procedure should further reduce any disparities among reviewer work loads.

The PHS concurred with our recommendation to revise the "first-in, first-reviewed" policy to ensure that ANDAs received in the review branch first are reviewed first. According to PHS, FDA has implemented this recommendation with its new random assignment system which will ensure that ANDAs, primarily unreviewed original applications, received in the branch first will be reviewed first. Under this policy, there are provisions for limited exceptions to the procedures. Any deviations which are not explicitly permitted under the guidelines for the random assignment policy must be approved by the division director and carefully documented. In addition, under the system of assigning applications, reasons for deviations from the review priority on the reviewer's queue must be documented at the time the exception is made.

The PHS agreed with our recommendation to develop specific written guidelines for reviewing chemists on the proper way for an ANDA to be reviewed. On December 30, 1991, the Director, OGD, issued a draft chemistry reference document for all reviewers and their supervisors. This document is being revised and OGD expects to finalize it in September 1992.

The PHS stated that in addition to the draft document, policy and procedure guides have been available to reviewing staff since 1989. The PHS stated that at least 12 of these guides are directly relevant to the scientific review of applications. Our follow-up audit work showed that many of OGD's policy and procedure guides actually had little relevance to the scientific review of ANDAs. The PHS also cited guide #28-90 as an example of a guide focused on the comprehensive review of ANDAs. Our follow-up audit showed, however, that the purpose of guide #28-90 is to expedite the review process.

The PHS concurred with our recommendation to establish a quality control review system outside of OGD to ensure the propriety of individual ANDA reviews and the integrity of the ANDA review process. The PHS stated that this was implemented in 1991, when OGD assigned responsibility for performing quality control assessments of seledted chemistry reviews to the Associate Director for Chemistry. In response to suggestions from OIG and others that the quality control function be separated from OGD, the Associate Director for Chemistry was assigned from OGD to the Office of the Director of CDER. The CDER management will conduct an independent review of this individual's performance. Pending establishment of this CDER-wide program, the Associate Director for Chemistry will perform quality control assessments of selected ANDA chemistry reviews.

The PHS concurred that, at the time of our May 12, 1992 draft report, the generic drug approval process still had deficiencies that constituted a material weakness under FMFIA. However, in its comments, PHS stated that FDA had implemented actions to address both the OIG's May 12, 1992 recommendations and the Commissioner's commitments to OMB. The PHS indicated that because of such progress, it planned to request the HHS Management Oversight Council, which is responsible for resolving FMFIA issues, to remove the generic drug approval process from HHS' list of material weaknesses.

While FDA has taken positive steps to address the serious deficiencies that constitute a material weakness disclosed in our August 1989 report and May 12, 1992 draft follow-up report, actions still remain to be taken to fully address this weakness. Only one corrective action has been fully implemented--the random assignment of applications. As for the

other two recommendations, regarding the development of a reference document for reviewers and implementation of a quality control review system, FDA is still in the process of implementing these actions.

Consistent with the fact that full implementation of corrective actions underway and planned is not expected to be completed until some future date, HHS should continue to report the generic drug application review process as a material internal control weakness under the provisions of the FMFIA. *In* addition, although OMB has deleted the generic drug application review process from the high-risk list, failure to meet the commitments made by the Commissioner may result in the review process being returned to the high-risk area.

The **HHS'** FMFIA policy requires that a detailed internal control review be conducted within 1 year after a material weakness is reported as being corrected. Such an internal control review will provide the Management Oversight Council with the information needed to determine if the generic drug approval **process'** weakness has in fact been corrected. Accordingly, FDA should conduct an internal control review after all corrective actions pertaining to the generic drug approval process have been completed.

We would appreciate being advised within 60 days on the status of corrective actions taken or planned on each recommendation. Should you wish to discuss the issues raised by our review and recommendations, please call *me* or your staff may contact Daniel W. Blades, Assistant Inspector General for Public Health Service Audits, at (301)443-3583.

bcc:
OIG/ES
Reading File - OAS
Reading File - PHSAD

PHSAD/ERADISH/JLJ - 08/26/92 FILE: 2GENER.RPT

APPENDIX

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 2 4 1992

Assistant Secretary for Health

Office of Inrpactot General (OIG) Drrf t Report "Follow-Up Review of the yood and Drug Administration's (IDA) Generic Drug Approval Process"

Inspector General, 08

Attached are the Public Health Service's comment8 on thesubject OIG report. We concur with each of the report'8 recommendation8 and our comments delineate the stepswehave taken to implement them.

We are pleartd to report thrt the recommendations contained in this report and the commitments made last December by the Commissioner of Food and Drugr to the Deputy Director of the Office of Management ● nd',Budget have been fulfilled. These commitments were for corrective ● ctionr to address problem8 in the generic drug approval process. FDA now har 'in place policies and procedure8 to ensure the random assignment of generic drug application8 and adherence to the "firrt-in, first-reviewed" policy; facilitate the uniform and consistent review of application8 through the use *of* reviewer guidelines; and perform quality control aasessmentr of generic drug application reviews.

/s/ James O. Mason

James O. Mason, M.D., Dr.P.H.

Attachment

cc:
ASH
ES/PHS
DASHMO
OM, Rm. 17-19, Parklawn
ORM, Rm. 17A-13, Parklavn
DFM. Rm. 17A-13. Parklawn

OH 13098

PUBLIC HEALTH SERVICE (PHS) COMMENTS ON THE OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT "FOLLOW-UP REVIEW OF FDA'S GENERIC DRUG APPROVAL PROCESS", A-15-91-00025

General Comments

The OIG conducted its field work on this review from April 1 to September 30, 1991. In the months following this review, PHS' Food and Drug Administration (FDA) and its Center for Drug Evaluation and Research (CDER) have taken additional steps to address all issues raised by OIG in this report. As a result, the recommendations made by OIG either have been or are being implemented at this time.

We are pleased to report that the commitments made by the Commissioner of Food and Drugs in December 1991 to the Deputy Director, Office of Management and Budget (OMB) have been fulfilled. These commitments were to: (1) finalize new policies and procedures for the assignment of generic drug applications, (2) finalize a reference document to facilitate the chemistry review of abbreviated new drug applications (ANDA), and (3) assess the concept and feasibility of a quality control review system. The following paragraphs describe the actions taken to fulfill each of these commitments.

Regarding the first commitment, a December 30, 1991 memorandum from the Director, Office of Generic Drugs (OGD) initiated implementation of a policy for the random assignment of ANDAs. Copies of this memorandum were provided to OGD's chemistry staff. The memorandum started a series of steps which resulted in the full implementation of random assignment'procedures effective June 8, 1992. This policy effectively removes any subjectivity in the assignment of ANDAs based on the concept of a chemistry review branch queue of unassigned applications. The oldest pending unreviewed original application in the branch queue will be assigned to the next available reviewer, subject to limited exceptions such as new reviewers, conflicts-of-interest by virtue of prior employment, and applications requiring special expertise. Any deviations from this policy must be approved by the appropriate supervisor and carefully documented.

In reference to the second commitment, FDA issued a draft chemistry reference document, dated December 30, 1991, for all chemistry reviewers and their supervisors. This document identifies the elements of a review of the chemistry, manufacturing, and controls portion of an ANDA. It facilitates the review process by indicating which parts of the Food, Drug, and Cosmetics Act; Code of Federal Regulations; OGD Policy and Procedure Guides; and other FDA documents relate to each element of a review. OGD is currently revising the draft to conform section number references to the regulations implementing Title I of the Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417, which were published in April 1992. OGD

expects to issue this chemistry reference in final in September 1992.

Finally, the third commitment has also been met. On December 30, 1991, the Associate Director of Chemistry, OGD, CDER, was designated to perform quality control assessments of selected OGD chemistry reviews. This individual was assigned to the Office of the Director, CDER, to enable Center management to conduct an independent review of his performance.

QIG Recommendation

We recommend that the Assistant Secretary for Health direct the FDA Commissioner to:

1. Modify the **ANDA** assignment method to remove the opportunity for branch chiefs to subjectively assign **ANDAs** to reviewers.

PHS Comment

We concur that the **ANDA** assignment system should provide a reasonable assurance that the opportunities to misuse and manipulate the system have been corrected. FDA has implemented this recommendation with a new policy that effectively removes any subjectivity in the assignment of **ANDAs.**

In a memorandum dated December 30, 1991, the Director, OGD, initiated a series of steps which resulted in the full implementation, on June 8, 1992, of a new policy for the random assignment of **ANDAs.** This policy provides for the assignment of **ANDAs,** primarily unreviewed original applications, in the order in which they are received in the branch. The oldest applications in the branch queue are assigned to the next available reviewer, subject to limited exceptions such as potential conflict-of-interest by virtue of prior employment, or applications requiring special expertise. The policy also helps to alleviate workload imbalances that might occur when the review chemists work from individual queues.

The new policy and procedures further reduce the opportunity to show partiality to applicants by building on controls previously in place. For example, the report indicated that it was possible for a chemistry reviewer to perform a superficial initial review of one firm's **ANDA** while performing a comprehensive review of another's. Thus, depending on the situation, giving advantage to one firm over the other. We disagree with this assertion.

The OGD has had guidance and controls in place for many months that act to prevent superficial review of **ANDAs.** Policy and Procedures Guide #28-90 requires that reviewers conduct a comprehensive review of an **ANDA** before issuing a not approvable

letter. The not approvable letter must contain a full statement of all deficiencies.

In order to enforce this guidance, OGD's first-line supervisors are directed to ensure that the chemists' reviews are comprehensive, address the major components of the ANDA, and that the resulting action letters reflect the complete review. Following this initial review, the Directors of OGD's two Divisions of Chemistry examine the chemistry reviews to ensure that they are comprehensive and adhere to CDER and OGD policies. Lastly, the Associate Director for Chemistry, who reports to CDER management, conducts an independent quality control audit of selected chemistry review to provide a third level of control.

The OIG report also expressed concern that, under OGD's former procedures, consideration was not given to a chemist's backlog when assigning ANDAs for review. To support its position, the report cited examples of the backlogs of applications ranging from S to 53 for different chemists.

A chemist's workload consists of ANDAs, supplements, and annual reports. All of these were taken into account by branch chiefs when assigning work. In addition, branch chiefs considered these additional critical factors:

- The number of strengths for the applications in the queue. Applications submitted prior to January 1, 1991, correspond to only one strength, while subsequent applications typically respond to two or more strengths. Usually, each chemist has a combination of applications submitted under the prior and new policies.
- The speed in which a chemist performs a review.
- The chemist's expertise.
- The complexity of applications in the chemist's queue. For example, one chemist's queue of five applications requiring complex, lengthy reviews may have required as much time as another's queue of more applications that needed more straightforward reviews.

A May 1992 OGD review of pending applications among chemists indicated that the widest range of backlogs of applications ranged from 2 to 14 for one branch.

The OIG's concern regarding reviewer backlog and assignment of applications is no longer relevant under OGD's new random assignment system.

OIG Recommendation

2. Revise the "first-in, first-reviewed" policy to ensure that ANDAs that *are* received in the review branch first are reviewed first.

PHS Comment

We concur. FDA has implemented this recommendation with its new random assignment system which will ensure that ANDAs, primarily unreviewed original applications, received in the branch first will be reviewed first. Under this policy there are provisions for limited exceptions to the procedures. An example of a special circumstance that could require deviation from the "first-in, first-reviewed" policy would be applications which require special reviewer expertise, such as metered dose inhalers. Any deviations which are not explicitly permitted under the guidelines for the random assignment policy must be approved by the division director and carefully documented.

In addition, under the system of assigning applications, reasons for deviations from the review priority on the chemist's review queue reflecting OGD's "first-in, first-reviewed" policy must be documented at the time the exception is made. Any exceptions are reported to the branch chief who documents the incident and discusses this topic during regularly scheduled meetings with the division director.

OIG Recommendation

3. Develop specific written guidelines for reviewing chemists on the proper way for an ANDA to be reviewed.

PHS Comment

We concur. FDA is implementing this recommendation. On December 30, 1991, the Director, OGD, issued a draft chemistry reference document for all chemistry reviewers and their supervisors. This document supplements existing policies and procedures and further ensures the consistent and comprehensive review of applications. It identifies the elements of a review of the chemistry, manufacturing and controls portion of an ANDA or abbreviated antibiotic application. It facilitates the review process by indicating which parts of the Federal Food, Drug, and Cosmetic Act, the Code of Federal Regulations, OGD Policy and Procedure Guides, and other CDER or FDA documents relate to each element of a review. OGD's training branch is using this document in its curriculum to train new chemists.

Currently OGD is revising this draft document. The revised chemistry reference document will conform section number

references to the regulations implementing Title I of the Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417. These implementing regulations were published on April 28, 1992. As stated above, OGD expects to issue this chemistry reference document in final in September 1992.

In addition to the chemistry reference document, OGD has had Policy and Procedure Guides available for its reviewing staff since 1989. At least 12 of these guides are directly relevant to the scientific review of applications.

OIG Recommendation

4. Establish a quality control review system outside of OGD to ensure the propriety of individual **ANDA** reviews and the integrity of the **ANDA** review process.

PHS Comment

We concur. FDA has implemented this recommendation. In 1991, **OGD** assigned responsibility for performing quality control assessments of selected chemistry reviews to the Associate Director for Chemistry. In response to'suggestions from OIG and others that the quality control function be separated from OGD, the Associate Director for Chemistry was assigned from OGD to the Office of the Director of CDER. CDER management will conduct an independent review of this individual's performance.

The CDER is in the initial stages of developing a broader quality assurance function that will cover reviews performed of both **ANDAs** and New Drug Applications (NDA). Pending establishment of this CDER-wide program, the Associate Director for Chemistry will perform quality control assessments of selected **ANDA** chemistry reviews.

OIG Recommendation

5. Continue to report the absence of adequate internal controls in the generic drug approval process as a material weakness under the Federal Managers' Financial Integrity Act **(FMFIA)** until such time as all recommended improvements have been fully implemented.

PHS Comment

We concur that at the time the OIG report was prepared, the generic drug approval process still had deficiencies that constituted a material weakness under **FMFIA.** However, our response to this OIG report demonstrates that all of the OIG recommendations, as well as the Commissioner's commitments to OMB, have been fully implemented. Therefore, we will notify the

Departmental Management Oversight Council (Council) that appropriate actions have been taken to correct the material internal control weakness in this program area. We will request that the Council declare this material internal control weakness corrected and the generic drug approval process be removed from the Departmental list of internal control weaknesses reported under **FMFIA.**