Memorandum

Date OCT 26 1992

From Bryan B. Mitchell
Principal Deputy Inspector General

Subject Follow-up Review of the Food and Drug Administration's Generic Drug Management Information System (A-15-91-00026)

To James O. 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 report entitled, "Review of the Food and Drug Administration's Generic Drug Management Information System" (A-15-89-00063), issued on July 6, 1990. That report was the second in a series of reports issued by the Office of Inspector General (OIG) in the generic drug area when it became known 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. In our July 1990 report, we made recommendations on how the generic drug management information system (MIS) could be better used by FDA to improve management and oversight of the generic drug review and approval process.

Our follow-up review disclosed that although FDA has taken certain actions to implement the recommendations made in our July 1990 report, more needs to be done. We determined that the generic drug MIS still does not track, in elapsed days, important events throughout the entire application review process, nor does it provide the reasons for variances in the times needed by FDA to approve applications for the same drug products submitted by different firms. In addition, FDA's alternative method for maintaining data on generic drug application deficiencies--a one-time study--rather than entering deficiency data into the MIS at the time the application is being reviewed, does not provide the means to continuously analyze how the drug industry can improve the quality of applications. Our follow-up review further disclosed that, with one exception, the MIS data on assignments were accurate and up-to-date, and the MIS was used as the primary tool to estimate the staffing needs for reviewing applications. We have made several recommendations to further improve the generic drug MIS.

The Public Health Service (PHS), in its August 19, 1992 response to our draft report, generally concurred in principle with each of our recommendations, but disagreed with the specific measures we proposed for improving the generic drug MIS. The PHS comments have been incorporated into the Agency Comments and OIG 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 MANAGEMENT INFORMATION SYSTEM

OCTOBER 1992 A-15-91-00026

Memorandum

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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 report entitled, "Review of the Food and Drug Administration's Generic Drug Management Information System" (A-15-89-00063), issued on July 6, 1990. That report was the second in a series of reports issued by the Office of Inspector General (OIG) in the generic drug area when it became known 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 generic drug management information system (MIS) is designed to provide supervisors and senior management of FDA's Center for Drug Evaluation and Research (CDER) with the necessary information to track the current status of Abbreviated New Drug Applications (ANDA)[1] reviews and assignments, manage personnel workloads, compile statistics, and maintain qualitative information about each application received and its review. The generic drug MIS is part of CDER's VAXcluster, which is a computer network serving 35 to 40 CDER users.

In our July 1990 report, we made recommendations on how the generic drug MIS could be better used by FDA to improve management and oversight of the generic drug review and approval process. Specifically, we recommended that FDA:

-- use the MIS to produce additional information to enable management to track the progress of applications, in elapsed days, through the review

[1]Drug firms must submit ANDAs to FDA for approval to market generic drug products. 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.

process; and to compare and analyze variances in application approval times;

-- include in the MIS information on the type and frequency of deficiencies found during application reviews;

-- correct information in the MIS data base to accurately reflect the assignment of applications to reviewers;

-- use the MIS to determine how effectively its current generic drug resources are used and to more precisely determine future staffing needs; and

-- revise the comprehensive action plan for generic drugs to incorporate those actions necessary to correct weaknesses in the generic drug MIS.

This follow-up review disclosed that although FDA has taken certain actions to implement the recommendations made in our July 1990 report, more needs to be done. Our follow-up revealed that: (1) the generic drug MIS still does not routinely track, in elapsed days, important events throughout the entire application review cycle, nor does it provide the reasons for variances in the times needed by FDA to approve applications for the same drug products submitted by different firms; (2) FDA's alternative method for maintaining data on ANDA deficiencies--a one-time study--does not provide the means to continuously analyze how the drug industry can improve the quality of applications; (3) with one exception, the MIS data on assignments appeared accurate and up-to-date; (4) the generic drug MIS was used as the primary tool to estimate its staffing needs for reviewing generic drug applications; and (5) FDA has adequately tracked all recommendations made by OIG in the generic drug area to determine the status of corrective actions.

BACKGROUND

In June 1988, the Subcommittee on Oversight and Investigations (Subcommittee), House Committee on Energy and Commerce, received allegations of improprieties associated with the generic drug approval 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 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 FDA employees, and 8 companies have pleaded guilty or have been found guilty of fraud or corruption charges. The investigation is continuing.

These events led FDA to develop, in August 1989, a comprehensive plan to strengthen the procedures by which generic drugs are evaluated and approved, and to bolster FDA's capacity to identify and correct fraudulent practices that can affect the integrity of its review process. One of the highlights of the plan was FDA's commitment to strengthen program management and oversight of the generic drug program.

Since an important element of program management and oversight is an effective MIS, OIG conducted a review of FDA's generic drug MIS. In July 1990, we reported that FDA lacked an adequate MIS to effectively monitor the generic drug application review process. We also stated that an effective MIS, or management reporting system, should: (1) provide accurate, timely, and meaningful data to assist management in achieving the objectives of the organization; and (2) provide information in a timely manner so that managers can identify problems and take prompt corrective action to avert crisis situations.

In response to our report, FDA, through its parent agency, the Public Health Service (PHS), advised us in October 1990 that it concurred or partially concurred with all but one of the recommendations in our July 1990 report. The FDA did not agree with our recommendation that its comprehensive action plan[2] for generic drugs be revised to include actions necessary to correct MIS weaknesses since the status of these actions are tracked quarterly in a separate monitoring system until fully implemented.

The Office of Generic Drugs (OGD), located in FDA's CDER in Rockville, Maryland, reviews original ANDAs, their

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[2]On August 18, 1989, the Secretary of Health and Human Services and the former Commissioner of FDA announced a comprehensive action plan to address the serious deficiencies in the generic drug review and approval process. The FDA established a system to specifically track implementation of these actions. In addition, FDA established separate tracking systems to monitor implementation of OIG recommendations regarding the generic drug approval process and the generic drug MIS.

amendments[3] and supplements,[4] and determines their approvability based on medical and scientific data. 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 1991, OGD received 1,453 original and amended generic drug applications and approved 141.

OBJECTIVE, SCOPE AND METHODOLOGY

The objective of our follow-up review was to determine if FDA had implemented the recommendations made in OIG's report entitled, "Review of the Food and Drug Administration's Generic Drug Management Information System," issued on July 6, 1990. To achieve this objective we verified, to the extent possible, the corrective actions that PHS stated were taken or proposed in its October 1990 response to OIG's report and subsequent progress reports.

We interviewed OGD officials and obtained documents to gather information on the process used to track applications through the review process. To determine the accuracy of reviewer assignments, we compared MIS reports identifying application reviewers with current OGD staffing rosters. We also analyzed FDA's "Comprehensive Needs Assessment" and related documents to determine the process used to estimate staffing requirements for the generic drug application review process. Finally, we reviewed two reports prepared by FDA on (1) chemistry and manufacturing deficiencies, and (2) labeling deficiencies contained in generic drug applications. These reports were prepared as an alternative to our recommendation that deficiencies identified in generic drug applications be included in the MIS.

The PHS, in its response to our draft report, generally concurred in principle with each of our recommendations, but disagreed with the specific measures we proposed for improving the generic drug MIS. The PHS comments pertaining to our recommendations, dated August 19, 1992, have been incorporated

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

[4]A firm must submit a supplemental application, or supplement, to FDA in order to change the conditions which were agreed upon when the ANDA was approved. Some examples of supplements include changes in manufacturing or testing procedures, changes in composition of the drug, or changes in size or shape of the tablet. Supplements can be made only to an already approved application.

into the Agency Comments and OIG Response section of this report and are included in their entirety in the Appendix.

Our review, performed from September through December 1991, at 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 although FDA has taken certain actions to implement the recommendations made in our report, the MIS continues to need improvement so that it provides an effective tool for managers to ensure the integrity of the generic drug application review process. Our evaluation of FDA's implementation of each of our recommendations is presented below. Our recommendations from the July 1990 report are followed by a description of FDA's corrective action and our evaluation of that corrective action.

OIG Recommendation: **Use the MIS to produce additional information to enable management to track the progress of applications, in elapsed days, through the review process; and to compare and analyze variances in application approval times.**

FDA Corrective Action: In responding to our July 1990 report, FDA agreed that the MIS should track the progress of applications in elapsed days through the review process. The FDA stated that, using reports generated from the MIS, the status of each application under review is discussed at least every 2 weeks by management at the division level and at least monthly at the office level. According to FDA, this provides a "real time" mechanism to monitor the progress of applications and identify and explain any variations in review time. The FDA stated that this system also enables management to identify problems before they result in the delay of an application.

OIG Follow up: We determined that although the MIS is generating reports showing the total number of elapsed days required to approve a generic drug from date of receipt to date of approval, it is not tracking the number of days needed to complete key events within the ANDA review process. Such key events include: the number of days needed by FDA to review each original ANDA and amendment submitted by a drug

firm; and the number of days needed by the drug firm to respond to each not approvable letter[5] issued by FDA.

The importance of capturing this key event data in the MIS is underscored by our finding that wide variances in review times continue, indicating possible application processing problems. During this follow-up review, we were able to identify in MIS reports examples of wide variances of processing times for the same drug. Although we could not determine from the reports why these variances occurred, it is possible that the variances are indicative of the type of preferential treatment accorded by several FDA employees to certain generic drug firms in the late 1980s. Such preferential treatment occurred by consciously approving certain firms' ANDAs faster than other firms' ANDAs, for the same drug. In our July 1990 review, we found similar wide variances in the time required to approve applications for the same drug product submitted by different companies.

The table below shows examples we identified during our follow-up review of extremely wide variances in approval times for the same generic drug.

Comparison of ANDA Approval Times

NAME OF DRUG	DATE ANDA RECEIVED	DATE ANDA APPROVED	DAYS NEEDED FOR APPROVAL
ALBUTEROL SULFATE			
Firm A	02 MAY 88	31 JAN 91	1004
Firm B	22 APR 88	07 APR 89	350
FENOPROFEN CALCIUM			
Firm C	29 JAN 88	30 APR 91	1187
Firm D	20 JAN 88	22 AUG 88	215
SULINDAC			
Firm E	21 MAY 87	17 APR 91	1427
Firm F	06 AUG 87	23 MAY 88	291
TRAZODONE HYDROCHLORIDE			
Firm G	03 JUL 86	27 FEB 91	1700
Firm H	16 SEP 86	11 DEC 87	451

[5]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 firm's response to a not approvable letter is called an amendment to the original ANDA.

While we recognize that all ANDAs cannot be approved in the same amount of time, the extremely wide variances in approval times should be tracked and analyzed by management. Such analyses would be particularly useful in providing early warning of potential application processing problems.

OIG Recommendation: **Include in the MIS information on the type and frequency of deficiencies found during application reviews.**

FDA Corrective Action: The FDA agreed with the intent of this recommendation but chose to implement it by performing a study of not approvable letters prepared by reviewers as opposed to permanently incorporating the information in the MIS.

OIG Follow up: We determined that although FDA has studied ANDA deficiencies, it would benefit from capturing this data on a routine basis in its generic drug MIS. Instead of performing a special one-time study of not approvable letters, the deficiency data in the MIS would be readily available to, for example, routinely inform drug firms of their ANDA problems.

The FDA conducted its ANDA deficiency study in two phases. The results of the first phase, which focused on chemistry and manufacturing deficiencies, were communicated to the industry at a September 24, 1990 briefing and published in March 1991. The second phase, which focused on labeling deficiencies, was completed in September 1991. The FDA announced the availability of the study report in various trade journals and at meetings. The report is available to the industry and others through FDA's dockets management branch.

We believe that FDA should reconsider our recommendation to include ANDA deficiency data in the generic drug MIS. This system would enable FDA to easily and routinely summarize a particular firm's or all firms' deficiencies at any given time for prompt feedback to the firms. Deficiency data should be communicated directly to each firm with the goal of receiving an acceptable ANDA from each firm on its first submission. A former Commissioner of FDA stated on several occasions that, "The quality of the application submitted to FDA remains the single most important factor influencing the speed of review and approval of the drug."

Recommendation: **Correct information in the MIS data base to accurately reflect the assignment of applications to reviewers.**

FDA Corrective Action: The FDA concurred with this recommendation and stated it has corrected the information in

the generic drug MIS data base reflecting the assignment of applications to specific reviewers. According to FDA, CDER instituted a policy to ensure that the assignments listed in the generic drug MIS are kept up-to-date. This policy requires each branch chief in OGD to obtain a MIS-generated status report of pending assignments. The FDA stated that on a biweekly basis, this report is used by the branch chiefs to discuss with each reviewer the status of assignments, discrepancies between the MIS report and actual situation, resolution of problems and, if warranted, the correction to the MIS data base.

OIG Follow up: Our analysis of MIS monthly assignment reports generated during our follow-up review indicated that the data were mostly accurate. However, in our review of an MIS assignment report, dated October 22, 1991, we identified some inaccurate reviewer assignment data. In the report, which listed the names of 26 reviewers who were processing 470 ANDAs, we noted that 9 of these ANDAs were listed as assigned to a reviewer who had resigned from OGD on October 4, 1991. The OGD officials told us they were aware of this situation and stated they planned to reassign the former reviewer's ANDAs and update the MIS.

This situation is similar to that found during our July 1990 review when we determined that, according to the MIS, ANDAs were assigned to employees who were no longer with FDA. This condition occurred because the OGD branch chiefs did not promptly reassign pending ANDAs to current reviewers and enter this data into the MIS. We believe that failure to promptly reassign applications and properly update the MIS could adversely affect the timely processing of ANDAs and possibly penalize drug firms whose ANDAs are not being reviewed.

OIG Recommendation: Use the MIS to determine how effectively its current generic drug resources are used and to more precisely determine future staffing needs.

FDA Corrective Action: The FDA concurred with this recommendation and stated that the generic drug MIS is now used to monitor staff workloads of original applications, amendments, supplements and their actions on a monthly and yearly basis. The FDA stated that the MIS provides management with the necessary information to determine how effectively its resources are being used and to predict future staffing needs.

OIG Follow up: As suggested in our July 1990 report, FDA has used its MIS to project the number of ANDAs that would be received based on the number of brand name drugs coming off patent through 1997. According to FDA, the MIS was used to

determine the number of ANDA reviews that should be completed by each reviewer in a given period of time. Based on its analysis of projected ANDAs and reviewer productivity, we believe FDA can realistically estimate its staffing needs.

The FDA has also factored into its resource estimates the need to reduce its current backlog of over 500 ANDAs and to terminate a project in which offices outside OGD are assisting in the review of ANDAs. The FDA plans to periodically re-evaluate its staffing needs for generic drug reviews.

OIG Recommendation: Revise the comprehensive action plan for generic drugs to incorporate those actions necessary to correct weaknesses in the generic drug MIS.

FDA Corrective Action: The FDA did not concur with this recommendation. It believes its comprehensive action plan does not need to be revised since the plan was designed to address deficiencies in the generic drug approval process. The FDA stated that it would develop a separate action plan to specifically track the implementation of recommendations for the generic drug MIS.

OIG Follow up: Although FDA did not agree to revise its comprehensive action plan to include those actions necessary to correct MIS deficiencies, we determined that it had developed a separate action plan to sufficiently monitor its progress in implementing the OIG generic drug MIS recommendations. The FDA tracks the progress of these recommendations on a quarterly basis.

CONCLUSIONS

The FDA's generic drug MIS, as currently designed, does not provide managers all the information needed to routinely assess and ensure the integrity of the generic drug application process. Accordingly, FDA needs to improve its generic drug MIS so that it offers up-to-date, accurate, and sufficient data for managers to effectively oversee the generic drug application review process.

Currently, the generic drug MIS does not provide managers with information needed to routinely track, in elapsed days, the time needed to complete certain events in the ANDA review process. These events include the number of days needed by FDA to review an original ANDA and each amendment to that ANDA submitted by a drug firm, and the number of days needed by the drug firm to respond to each not approvable letter issued by FDA. By tracking the number of days needed to complete these events, managers could immediately become aware of problems and take corrective action. For example, if two original ANDAs are received in FDA at the same time from two firms, but

one firm receives its first deficiency letter in 120 days while the other firm does not receive its first deficiency letter until 200 days after its submission, FDA should immediately determine the reasons for the difference and take appropriate action.

We believe that FDA should include ANDA deficiency data in the generic drug MIS. This would enable FDA to easily and routinely summarize a particular firm's deficiencies at any given time for feedback to the firm. Through letters, conferences, briefings and other methods, FDA should strive to improve the quality of ANDAs with a goal of providing firms information needed to develop and prepare acceptable ANDA submissions.

With regard to the one instance where we found that MIS reports indicated that ANDAs were being reviewed by an employee who no longer works in OGD, we believe that when an employee leaves OGD, that employee's ANDAs should promptly be assigned to another employee and this reassignment accurately reflected in MIS reports. All MIS reports indicating the status of ANDAs pending review in OGD should reflect only the names of current employees.

RECOMMENDATIONS

We recommend that you direct the Commissioner of FDA to:

-- ensure that the generic drug MIS tracks, in elapsed days, the time needed by FDA and the drug firms to complete key events throughout the entire application review process;

-- include ANDA deficiency data in the generic drug MIS; and promptly communicate deficiency summaries directly to drug firms with the goal of assisting firms to develop and prepare acceptable ANDA submissions; and

-- ensure that all generic drug MIS reports pertaining to application assignments are updated biweekly and reflect only the names of current employees.

AGENCY COMMENTS AND OIG RESPONSE

The PHS, in its August 19, 1992 memorandum commenting on our draft report, generally concurred in principle with each of our recommendations, but disagreed with the specific measures we proposed for improving the generic drug MIS. Its complete response is included in its entirety in the Appendix to this report and certain responses are paraphrased in this section.

Tracking Key Events

The PHS concurred in principle with our recommendation that FDA ensure that the generic drug MIS tracks, in elapsed days, the time needed by FDA and the drug firms to complete key events throughout the entire application review process. However, in accordance with its October 29, 1990 comments on our original MIS report, PHS continues to believe that including the additional elements recommended by OIG would involve the capturing, entering, analyzing, and interpreting of data which would further burden but not improve the oversight of the review process. The PHS believes that CDER's internal management monitoring system for the generic drug program satisfies the requirements of this recommendation.

The PHS noted that variations in the length of approval time for the same drug products may result from a number of legitimate factors including: (1) the submission of an application of such poor quality that several review cycles might be required; (2) delay in responding to a not approvable letter by OGD; (3) other priority work which takes up the time of the reviewer; and (4) delay caused by awaiting an outstanding clearance from FDA's field offices about a firm with good manufacturing practice violations, or potential fraud issues. The PHS believes that as a result of measures such as its random assignment policy, ANDA approval tracking committee and barcoding system, the extent to which these differences can occur has been minimized and no other action is necessary.

We agree that a number of legitimate factors can result in variations in the length of approval time for the same drug products. We are also encouraged by the measures FDA has taken to minimize the extent to which these factors contribute to differences in approval times. However, as illustrated by the situation that occurred in the late 1980s, variations in the length of approval time can also result from preferential treatment being given to a specific drug firm during the application review and approval process. The FDA needs to be able to determine if such situations are occurring and having an impact on the drug approval process.

During our June 1992 exit conference, OGD officials recounted the time-consuming and labor-intensive task they had just completed to determine the reasons for the difference in two drug firms' approval times. This task required special MIS programming and a comprehensive review of application files. If FDA had programmed the MIS to track key events in the application process, OGD management would be readily aware of the reasons for variances in approval times as they occur and

the need for such labor-intensive efforts would be eliminated. Further, FDA would be able to take timely action to correct any preferential treatment situation that may be occurring.

Deficiency Data

The PHS concurred with the objective of our recommendation to include ANDA deficiency data in the generic drug MIS; and promptly communicate deficiency summaries directly to drug firms with the goal of assisting firms to develop and prepare acceptable ANDA submissions. The PHS believes that the quality of applications submitted to FDA is a major factor in influencing the speed of review and approval.

The results of FDA's October 1990 study of generic drug deficiencies identified approximately 1,200 deficiencies based on 90 not approvable letters. According to PHS, the deficiencies were numerous and had several levels of meaningful detail. The PHS believes that some of this deficiency information could be captured in a general sense in the MIS, but that it would not provide a level of detail useful to the generic drug industry. The PHS agreed, however, that additional efforts are needed to educate industry, and stated that FDA will continue to perform occasional studies to identify and organize deficiency information, and communicate this to the industry.

The PHS stated that deficiencies are currently being communicated to industry regularly and provided examples of the methods used to carry out these communications. We acknowledge FDA's efforts to communicate with the drug industry to improve the quality of applications submitted to FDA. However, we found that the quality of applications from drug companies does not appear to be improving. For example, during the period from August 1990 to July 1991, FDA received a monthly average of 4.09 amendments for each original ANDA submitted, as compared to a monthly average of 4.96 amendments for each original amendment submitted between August 1991 and July 1992.

Given that the quality of applications does not appear to be improving, we believe PHS needs to reconsider our recommendation to include deficiency data in the generic drug MIS. According to FDA, the costs of modifying and maintaining the MIS to include a level of necessary detail for meaningful analysis would be considerable and a more cost effective method is needed to achieve this objective. However, the inclusion of this data would allow OGD management to be aware of any firm's deficiency history at any point in time and eliminate the labor-intensive efforts needed to manually review not approvable letters. It would also allow FDA to work with individual firms to increase the receipt of

approvable drug applications. Therefore, we continue to believe that the benefits of having such data included in the generic drug MIS would outweigh the costs.

Updating Reports

The PHS concurred with our recommendation to ensure that all drug MIS reports pertaining to application assignments are updated biweekly and reflect only the names of current employees. According to PHS, FDA is meeting the intent of this recommendation through its new random assignment procedures. The PHS stated that amendments are treated differently and normally go to the prior reviewer. However, if that reviewer leaves, the assignment designation will be removed from the MIS within 2 weeks and the amendment is treated like an original unreviewed application, i.e., it remains in the branch queue as unassigned, until a reviewer is available to work on it.

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/ESR-JLJ - 10/06/92 FILE: MIS-FIN.RPT

APPENDIX

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date . AUG 19 1992

From **Assistant Secretary for Health**

Subject Office of Inspector General (OIG) Draft Report "Follow-Up Review of the Food and Drug Administration's (FDA) Generic Drug Management Information System (MIS)"

To Acting Inspector General, OS

Attached are the Public Health Service's comments on the subject OIG draft report. We concur in principle with the report's recommendations and support the objectives that would be achieved through implementation of them.

Our comments describe the FDA systems, policies and procedures that complement the generic drug MIS and provide FDA management with the necessary information to track the status of generic drug applications under review, manage personnel workloads, compile statistics, and provide qualitative information about each application.

James O. Mason

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

Attachment

IO	
PDIG	✓
DIG-AS	✓
DIG-EI	
DIG-OI	
AIG-MP	
OGC/IG	✓
EX SEC	
DATE SENT	8/20

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PUBLIC HEALTH SERVICE (PHS) COMMENTS ON THE OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT "FOLLOW-UP REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S (FDA) GENERIC DRUG MANAGEMENT INFORMATION SYSTEM," A-15-91-00026

The objective of this OIG follow-up review was to determine if FDA had implemented the recommendations made in OIG's report entitled "Review of FDA's Generic Drug Management Information System (MIS)," issued on July 6, 1990.

The OIG found that: (1) FDA has adequately tracked all recommendations made by OIG in the generic drug area to determine the status of corrective actions; (2) with one exception, the MIS data appeared accurate and up-to-date; and (3) the generic drug MIS was used as the primary tool to estimate staffing needs for reviewing generic drug applications. However, OIG states that the MIS neither routinely tracks, in elapsed days, important events in the generic drug approval process, nor does it provide the reasons for variances in the times needed by FDA to approve the same drug products submitted by different firms. Also, OIG notes that FDA's method for obtaining data on abbreviated new drug application (ANDA) deficiencies, a one-time study, does not provide the means to continuously analyze how the drug industry can improve the quality of its applications.

OIG Recommendation

1. Ensure that the generic drug MIS tracks, in elapsed days, the time needed by FDA and the drug firms to complete key events throughout the entire application review process.

PHS Comment

We concur in principle with this recommendation and believe that the internal management monitoring system for the generic drug program that is operated by FDA's Center for Drug Evaluation and Research (CDER) satisfies the requirements of the OIG recommendation.

In our October 29, 1990, comments on the final version of OIG's original MIS report, we explained that important events during the review process were tracked effectively through regular FDA management oversight meetings. We continue to believe that including the additional elements recommended by OIG would involve the capturing, entering, analyzing, and interpreting of the data which would further burden the review process without improving the oversight of the process.

The OIG noted that all applications for the same drug product do not go through the review and approval process in the same length of time. There are a variety of reasons why applications have different approval times. For example:

- The firm may submit an application of poor quality that

may require several review cycles. The FDA Office of Generic Drugs (OGD) continually strives to inform the industry and individual applicants on ways to improve the quality of submissions. For additional information, see the PHS response to recommendation number 2 below.

- The firm may delay in responding to a not approvable letter issued by OGD. OGD monitors undue delays and calls the firm if it takes more than 45 days to respond with a minor amendment.

- The chemist may have to set aside a review of a new ANDA or major amendment to address higher priority work, such as minor amendments.

- The chemist may be awaiting an outstanding clearance from FDA's field offices about a firm with good manufacturing practice violations, or potential fraud issues.

Despite these legitimate reasons for variances in ANDA approval times, FDA recognizes that there are factors over which OGD has some control that could contribute to variations in approvals of applications for the same drug product from different applicants. Therefore, FDA has instituted several measures to minimize the extent to which these factors contribute to time differences. Some of these measures are described below:

- Random assignment policy. OGD has implemented the new random assignment system that generally will ensure ANDAs received in a chemistry branch first will be reviewed first. This policy was instituted at the urging of the OIG.

- ANDA approvals tracking committee. Twice a month, OGD's senior managers meet to review the status of ANDAs and abbreviated antibiotic drug applications (AADA) that have been recommended for approval by the review chemists. The Committee identifies and addresses problems, such as microbiology or compliance issues, that could be impeding approval. Applications ready for approval are carefully monitored to facilitate final administrative reviews and signatures.

- Barcoding system. OGD initiated a barcoding system after its October 1991 relocation to secure facilities which resulted in the consolidation of three document rooms. The system tracks the location of approximately 48,000 ANDA and AADA jackets and related documents. It tracks the flow of applications into and out of the document room and inventories applications outside the document room, using portable laser scanners, on a weekly

basis. Using this system, OGD review staff are able to locate documents when needed, thereby eliminating one of the causes of variations in approval times.

- o Monitoring review of applications. OGD chemistry review branch chiefs routinely use the MIS to monitor the progress of review of applications. They meet monthly with the division directors to discuss review progress and adherence to the OGD's policies, including the random assignment procedures.

- o Other measures. Measures intended to address potential vulnerabilities in the review process are also described in PHS' July 24, 1992 comments on the OIG draft report "Follow-up Review of FDA's Generic Drug Approval Process," A-15-91-00025. These measures include: finalizing a reference document to facilitate the chemistry review of ANDAs, and performing quality control assessments of generic drug application reviews.

The PHS believes no further action is necessary.

OIG Recommendation

2. Include ANDA deficiency data in the generic drug MIS; and promptly communicate deficiency summaries directly to drug firms with the goal of assisting firms to develop and prepare acceptable ANDA submissions.

PHS Comment

We concur with the objective of this recommendation to provide information to the industry to improve the quality of generic drug applications. We believe that the quality of applications submitted to FDA is a major factor in influencing the speed of review and approval. Nonetheless, we need a more cost effective way to achieve this objective.

In our October 1990 response to OIG's original MIS report, we noted that FDA was conducting a study of generic drug deficiency letters for the dual purposes of: (1) identifying deficiencies in the applications that contributed to their non-approval, and (2) organizing and communicating the findings and conclusions of this analysis to the drug industry with the hope that this would result in better submissions and shorter review times. We stated that informing the industry of the study's result would achieve the objective of the OIG recommendation.

The study was completed and identified approximately 1,200 deficiencies based on 90 not approvable letters. The deficiencies were numerous and had several levels of meaningful

detail. Some of this deficiency information could be captured in a general sense in the MIS, but that it would not provide a level of detail useful to the generic drug industry.

With respect to OIG's recommendation that FDA should modify its generic drug MIS, we note that deficiencies are currently being communicated to industry regularly, and the costs of modifying and maintaining the MIS to include a level of necessary detail for meaningful analysis would be considerable. For example:

- Communicating Deficiencies. OGD communicates to the industry as a whole its findings about the types of deficiencies noted in applications by giving speeches at trade association meetings, issuing reports on studies of deficiencies, and conducting workshops.

  In November 1991, OGD notified industry that it was tightening the pre-filing screening criteria that it began using in 1990. Since that time, the number of "refuse to file" letters has increased. More applications with significant deficiencies are being rejected at the outset. This practice should provide incentives to applicants to improve the quality of their submissions and may result in faster approval times because the applicant is informed early in the review process of gross deficiencies. The reasons for "refusing to file" these applications were compiled and sent to all generic firms in a letter dated July 1, 1992.

  Also, OGD communicates information on deficiencies to individual applicants by: (1) sending a not approvable letter in which it states the deficiencies noted in the review and may also suggestions ways to improve the submission; (2) meeting with individual firms to discuss technical issues about applications; and (3) telephoning firms to resolve minor deficiencies or technical issues.

- Modifying MIS. Regarding the coding of deficiencies in the MIS, the cost of categorizing and entering the deficiencies would be substantial. Based on the results of a 1991 study of 1,200 deficiencies in 90 not approvable letters, this effort would involve an average of 13 deficiencies for each of the approximately 100 not approvable letters OGD issues monthly. At a minimum, the pharmacologist, chemistry and labeling reviewer would have to consider the following criteria for each deficiency: (1) the part of the application affected, such as chemistry or labeling; (2) the type of deficiencies, such as stability testing or manufacturing instructions; and (3) the reason for the deficiency.

A brief description of each deficiency would be required to assist any meaningful interpretation of the data. A feasibility study would have to be done to determine, among other things, if the classifications of types of deficiencies used in the study are still appropriate. A major system design would need to be done, as well as extensive programming to change the MIS. The reviewers would have to be trained to classify and record information for data entry, and an on-going quality control system would have to be implemented to check for accuracy.

In summary, the cost to the agency to implement the OIG's recommendation would be considerable. These resources, if available, would be better spent in areas where the incremental benefit to the agency would be greater.

As indicated above, FDA uses a variety of effective methods to routinely communicate deficiencies to applicants. Although ANDA deficiencies are communicated to industry, PHS agrees that additional efforts to educate industry may be appropriate. Therefore, FDA will continue to perform occasional studies to identify and organize deficiency information, and communicate this to the industry.

OIG Recommendation

3. Ensure that all generic drug MIS reports pertaining to application assignments are updated biweekly and reflect only the names of current employees.

PHS Comment

We concur. FDA is meeting the intent of this recommendation through its new random assignment procedures.

Under the new random assignment policy, OGD will continue to assure MIS reports are up to date within reasonable time frames. Under this policy an original unreviewed application will not be assigned to a reviewer until he or she actually is available to begin work on it. Therefore, it will remain in a branch queue unassigned until a reviewer is available.

Amendments are treated somewhat differently. Although these are also placed in the branch queue, they normally go to the prior reviewing chemist. However, if that chemist leaves, the assignment designation will be removed from the MIS within two weeks and the amendment is treated like an original unreviewed application, i.e., it remains in the branch queue as unassigned, until a chemist is available to work on it.