
PERSPECTIVES OF DRUG MANUFACTURERS

ABBREVIATED NEW DRUG APPLICATIONS



OFFICE OF INSPECTOR GENERAL
OFFICE OF EVALUATION AND INSPECTIONS

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PERSPECTIVES OF DRUG MANUFACTURERS

ABBREVIATED NEW DRUG APPLICATIONS

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INSPECTOR GENERAL**

EXECUTIVE SUMMARY

PURPOSE

The purpose of this report is to describe the perspectives of selected drug manufacturers regarding the Food and Drug Administration's (FDA) review of market applications for generic products. This is one of several reports being issued by the Office of Inspector General (OIG) in connection with FDA's approval of generic drugs.

This report contains the accounts of manufacturers regarding their experiences and opinions of FDA's review of market applications for generic products. For maximum benefit, the reader should consider this information along with the results of independent analysis conducted by the OIG regarding FDA's approval of generic products.

BACKGROUND

Under the Federal Food, Drug, and Cosmetic Act ("the Act"), as amended, the FDA, U.S. Department of Health and Human Services, is responsible for approving new drugs before they can be marketed in the United States. The Act defines a new drug as "...any drug [that]...is not generally recognized...as safe and effective under the conditions prescribed, recommended, or suggested in the labeling...." (21 U.S.C. section 321.) The FDA is charged with ensuring that the drugs it approves are both safe and effective for its intended uses.

New drugs include both "innovator" drugs and "generic" drugs. Innovator drugs, or drugs newly discovered, are generally developed under patent by the manufacturer. Generic drugs, or copies of drugs currently on the market, are developed by competitors after a patent has expired, or if the innovator patent will not be infringed or is invalid. Unless a suitability petition has been approved exempting the manufacturer from this requirement, generic drugs must contain the same active ingredients and be manufactured in the same strength and dosage form as the innovator drug.

METHODOLOGY

To assess manufacturers' perspectives regarding FDA drug approval, the OIG invited 24 firms to discuss their experiences with, assessments of, and suggestions for improving FDA drug approval. All 24 firms agreed; the firms participating in the study are listed in appendix A.

Of the 24 firms listed, representatives of 16 discussed their professional experiences with the generic drug approval process. The results of those discussions are described in this report.

FINDINGS

Virtually all of the manufacturers we interviewed *consider FDA effective in ensuring that drugs entering the marketplace are safe and effective*. At the same time, the respondents were generally critical of FDA's drug approval process for generic products—much more so than the respondents we interviewed concerning FDA's approval of innovator drugs.

For each of the following, a majority of respondents in our survey believed that:

- o *FDA is ineffective in ensuring that safe and effective drugs enter the market in a timely manner;*
- o *FDA provides inadequate guidance on how to develop and submit a successful ANDA;*
- o *communication between the Agency and industry regarding ANDAs is often inadequate, ineffective, or untimely;*
- o *FDA is inconsistent when reviewing ANDAs and making decisions;*
- o *FDA provides insufficient justification for the decisions it makes on ANDAs;*
- o *it is difficult to appeal decisions made by the Agency on ANDAs; and*
- o *there is inadequate staffing at FDA, or inefficient use of staff, to deal with the current workload of ANDAs.*

Respondents *disagreed on whether two recent FDA initiatives, establishing the Office of Generic Drugs and creating an FDA Ombudsman, would help address the concerns they discussed*. Respondents did believe, however, that FDA should continue sampling drugs on the market, to ensure the quality of drugs sold to consumers. Finally, respondents *suggested changes in FDA generic drug approval*.

AGENCY COMMENTS.

The OIG briefed FDA officials on the findings and manufacturer recommendations from this survey. The FDA officials provided a number of clarifying technical comments to the report. A copy of the Agency's comments regarding the results of the survey and our briefing are attached at appendix B.

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INTRODUCTION

PURPOSE

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Until its patent expires, the manufacturer of the innovator drug enjoys a virtual monopoly in manufacturing and selling its patented invention. Manufacturers of the generic version of the drug generally price their product lower than the innovator firm's product to compete with other manufacturers producing generic versions of the drug and the innovator firm. The lower cost of generics can make them attractive to cost-conscious health care consumers and third-party payors.

The 1984 Drug Price Competition and Patent Restoration Act

In 1984, the Congress passed the Drug Price Competition and Patent Restoration Act, which amended the Act. Among other things, this law streamlined the requirements for approving generic products.

Prior to passage of the Drug Price Competition and Patent Restoration Act, manufacturers seeking to market a generic version of drug marketed between 1938 and 1962 could submit an abbreviated application to FDA to obtain approval of their product. Manufacturers seeking approval of generic versions of drugs marketed *after* 1962 were required to submit an application to FDA to demonstrate that the active ingredients in their product were both safe and effective, based either on their own clinical trials (described in a New Drug Application (NDA)) or on the basis of published reports of well-controlled studies (described in a “paper NDA”).

The Drug Price Competition and Patent Restoration Act allowed manufacturers to submit an Abbreviated New Drug Application (ANDA), rather than an NDA or “paper NDA” to obtain approval of the generic version of a drug marketed after 1962, as well as those marketed between 1938 and 1962. Since the generic contains the same active ingredients previously demonstrated safe and effective to the FDA by the innovator, Congress reasoned that there was no need for retesting. Rather, Congress required manufacturers of generic drugs to demonstrate that their product worked in the same way in the body as the innovator’s drug—in other words, that it is “bioequivalent.”

The ANDA differs from the NDA in that the manufacturer is not required to conduct and report results of animal and human clinical trials to demonstrate the drug’s safety and effectiveness. Instead, the manufacturer must include data in the ANDA to demonstrate that (1) the generic drug contains the same active ingredients as the innovator product; (2) the generic drug is identical in strength, dosage, and route of administration as the innovator product; and (3) the generic drug is bioequivalent to the innovator product.¹ (21 U.S.C. 355(j)(2)(A).) Because the manufacturer of a generic drug does not have to conduct the more costly and time consuming clinical trials required of the innovator firm, ANDAs are less costly for manufacturers to prepare and submit to FDA than NDAs.

Not surprisingly, FDA experienced a substantial surge in the number of ANDAs submitted to the Agency after passage of the 1984 law. According to FDA testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, the Agency has seen a threefold increase in number of both original ANDAs (those ANDAs submitted for the first approval of the manufacturer’s generic) and supplemental ANDAs (those ANDAs submitted to obtain approval in a change in manufacturing, labeling, or other aspect of the production and marketing of the drug) submitted to the Agency since 1984.²

Submitting and Reviewing ANDAs

When manufacturers submit an ANDA for FDA's review and approval, it must contain certain information. Recently FDA has issued a Proposed Rule which would implement the 1984 law. The FDA proposed that ANDAs submitted to the Agency include, among other things, the following: (1) an application form, containing identifying data such as the name and address of applicant, a statement of how the drug will be marketed, and the signature of an authorized official; (2) a discussion of the basis for the ANDA; (3) a discussion of conditions of use; (4) a listing of active ingredients of the drug; (5) a discussion of the route of administration, dosage form, and strength; (6) bioequivalence data; (7) a chemistry, manufacture, and controls section, describing the composition, manufacture, and specification of the drug substance and the drug product; and (8) proposed labeling. [54 Fed. Reg. 28,872, 28,921 (1989) (to be codified at 21 CFR 314.94) (proposed July 10, 1989).]

Once an application is submitted, FDA has 180 days to review an application and send the applicant either an "approved" letter, an "approvable" letter, or a "not approvable" letter. This 180-day period is referred to as the "review clock."

An "approval" letter means a written communication to the application from FDA approving an application. Only after receiving an "approval" letter from FDA may a manufacturer market the drug that is the subject of the application. An "approvable" letter means a written communication stating that the Agency *will* approve the application if certain conditions are met (such as changes in the manufacturing controls). A "not approvable" letter means that the Agency does not consider the application approvable due to deficiencies identified in the application.

During review, communication takes place between FDA and the applicant. Industry officials may request meetings with the Agency if such requests are made in advance and an agenda is agreed upon. The FDA offers an "end-of-review" conference to applicants after they receive an "approvable" or "not approvable" letter to discuss what steps the manufacturer must take to get the application approved.

Once an application is approved, certain changes may be made by the manufacturer in the course of manufacturing and marketing the drug. Depending on the type of change made (e.g., changes in drug substance or drug product that affect performance versus editorial change in labeling) the manufacturer must either submit (1) a supplement requiring FDA approval before changes can be made; (2) a supplement describing changes to FDA that have already been made; or (3) a description of the types of changes made in the next annual report to the Agency. Only information relating to the change must be included in the supplement.

Recent Concerns Regarding FDA Review of ANDAs

In the past year, substantial criticism has been directed at the FDA generic drug approval process. In 1988, the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, based on information it received from a generic drug manufacturer, asked the Office of Inspector General (OIG) and the United States Attorney to conduct an investigation into allegations of favoritism on the part of certain FDA officials responsible for reviewing and approving ANDAs. The OIG's investigation resulted in corruption charges and criminal convictions of three former FDA employees, three generic drug company officials, and two generic drug firms.

In the wake of the corruption charges, FDA began to target, review and test generic drug products and related ANDAs in an effort to ensure the integrity of these products. This review disclosed manufacturing deficiencies and fraud involving a number of generic drug firms and their products. Where fraud appeared likely, the FDA with the assistance of the OIG initiated additional criminal investigations which are continuing.

In August 1989, the OIG completed an audit of the generic drug approval program to identify weaknesses and vulnerabilities in the system which gave rise to the problems discussed above. The OIG audit team found, among other things, that FDA lacks adequate guidelines to ensure the consistent review of applications and needs a quality control system to ensure that applications are properly reviewed and that generic drug firms receive equitable treatment.³

Throughout 1989, there was an unusually high level of media and press attention devoted to concerns about the generic drug approval process. Reports appearing in major national newspapers and the pharmaceutical trade press in August and September 1989 (the time of our survey) focused on the corruption allegations and subsequent investigations undertaken by the FDA and OIG; the OIG audit findings and recommendations; and FDA's response, described below, which included procedural and organizational changes and product testing and site inspections affecting a large segment of the generic industry.

FDA Response to Concerns

In response to allegations of favoritism publicized by the Subcommittee, FDA conducted an internal assessment of the ANDA process in 1988. Among the reforms initiated as a result of this review were new procedures limiting and formalizing contacts between industry and reviewers. Industry representatives are no longer allowed to make unannounced visits; meetings are now held away from reviewer work space; and Consumer Safety Officers, rather than reviewers, answer calls from firms concerning the status of applications.

In 1989, FDA took additional steps to correct the opportunities for abuse in approving generic drugs and to reestablish public confidence in the safety of generic drugs. These steps included:

- establishing a new Office of Generic Drugs under a new management team;
- creating an ombudsman in the Office of Commissioner to mediate disputes between FDA and the firms it regulates;
- targeting, reviewing and testing generic drug products and related ANDAs; and
- conducting an internal audit of the generic drug approval process in accordance with the Federal Managers' Financial Integrity Act of 1982 (FMFIA).

METHODOLOGY

To assess manufacturers' perspectives regarding FDA drug approval, the OIG invited 24 firms to discuss their experiences with, assessments of, and suggestions for improving FDA drug approval. All 24 firms agreed; the firms participating in the study are listed in appendix A.

Of the 24 firms listed, representatives of 16 discussed their professional experiences with the generic drug approval process. The results of those discussions are described in this report.⁴

Previous work done by the Office of Planning and Evaluation, Office of the Commissioner, FDA, formed the framework for conducting this study. Prior studies titled Agency Impact Analyses (AIAs) examined the effect of FDA practices and procedures on a regulated industry by collecting and analyzing the perspectives of executives of some of the regulated firms.⁵

About the Interviews

The firms invited to participate in the OIG interviews were selected to ensure approximately equal distribution of firms experienced in generic drug and new drug approval. Respondents from seven firms had experience with both processes. Manufacturers interviewed were concentrated in New York, New Jersey, and Pennsylvania, although interviews also took place with manufacturers in Colorado, Delaware, Illinois, Ohio, and West Virginia.

Generally interviews were conducted with the chief executive officer, president, and/or regulatory affairs director and staff of the firms selected. A total of 49 individuals were interviewed. The 24 firms visited during the course of our study had by their own estimation submitted in excess of 450 investigational new drug applications, 150 new drug applications, and well over 1,000 abbreviated new drug applications and abbreviated antibiotic drug applications in the past 5 years.

Interviews were conducted in August and September, 1989. To conduct the interviews, all of which were conducted in person, the OIG used a structured discussion guide asking respondents about their experiences and opinions regarding various aspects of application

review and approval. Respondents were asked how they view guidance from the agency, communication with the agency, review of applications by the agency, and decision-making by the agency.

Because the manufacturers selected do not necessarily reflect a representative sample of all manufacturers, their views may or may not constitute a consensus opinion of all manufacturers. In addition, the OIG study team did not attempt to verify or validate the legitimacy of claims or concerns expressed by the firms. Consequently, we do not recommend specific action to the FDA based on the results of these interviews. Rather, we have presented the recommendations made by the manufacturers interviewed for FDA's information and consideration.

FINDINGS

Virtually all of the manufacturers we interviewed *consider FDA effective in ensuring that drugs entering the marketplace are safe and effective*. At the same time, the respondents were generally critical of FDA's drug approval process for generic products—much more so than the respondents we interviewed concerning FDA's approval of innovator drugs.

For each of the following, a majority of respondents in our survey believed that:

- o *FDA is ineffective in ensuring that safe and effective drugs enter the market in a timely manner;*
- o *FDA provides inadequate guidance on how to develop and submit a successful ANDA;*
- o *communication between the Agency and industry regarding ANDAs is often inadequate, ineffective, or untimely;*
- o *FDA is inconsistent when reviewing ANDAs and making decisions;*
- o *FDA provides insufficient justification for the decisions it makes on ANDAs;*
- o *it is difficult to appeal decisions made by the Agency on ANDAs; and*
- o *there is inadequate staffing at FDA, or inefficient use of staff, to deal with the current workload of ANDAs.*

Respondents *disagreed on whether two recent FDA initiatives, establishing the Office of Generic Drugs and creating an FDA Ombudsman, would help address the concerns they discussed*. Respondents did believe, however, that FDA should continue sampling drugs on the market, to ensure the quality of drugs sold to consumers. Finally, respondents *suggested changes in FDA generic drug approval*.

Each of these findings is discussed in more detail below.

Respondents believe that FDA is effective in ensuring that drugs entering the marketplace are safe and effective.

Fifteen of the 16 respondents who had experience with the generic drug approval process felt that FDA does an effective job in ensuring that drugs entering the market are safe and

effective. Most of the respondents felt that such assurance was FDA's charter or mandate and that the Agency took no shortcuts in meeting its obligations. "Look at the record," one manufacturer said. "With very few exceptions there have been no catastrophes." "I don't quarrel with the end result," said another respondent, "just the way they get there." Respondents viewed FDA as taking a "no risk" policy: "the process rewards people for creative ways of assuring that the most stringent standards are [imposed]."

For these reasons, most respondents (10) also believe that FDA review of ANDAs is thorough. "The review is very detailed," said one respondent. "Reviewers are known for looking for uncrossed t's and undotted i's." Other respondents saw the results as proof of thoroughness: "So far [we] haven't found anything that was grossly missed."

At the same time, respondents believe that FDA is ineffective at ensuring that safe and effective drugs enter the marketplace in a timely manner.

Ten of 16 respondents thought that FDA was ineffective in ensuring that safe and effective drugs enter the marketplace in a timely manner. Many attributed this lack of timeliness to FDA's emphasis on safety: "Timeliness isn't one of FDA's priorities," said one respondent. "[FDA] is much more concerned with [keeping] a bad product [off] the market.... The commissioner says one priority is to cut the backlog but reviewers are more concerned with making a mistake." Some respondents argued for a change in orientation by the agency: "FDA should help us get approval, not prevent or deter manufacturers [from getting our applications approved]," said one respondent."

Some respondents were perplexed that certain parts of the review that appear straightforward to them take, in their view, too much time. For example, the manufacturers we interviewed were critical of the time required to review and approve labels.

Respondents believe that the Agency provides inadequate guidance on how to develop a successful ANDA.

Nine of the 16 manufacturers interviewed believe that the guidance provided to them by the Agency on how to develop a successful ANDA is "inadequate." Manufacturers expressing this opinion argued that they needed more direction from the Agency in the form of standards and specifications before developing their ANDA. One respondent echoed the sentiments of several others when he said, "We need the blueprint ahead of time." Several manufacturers pointed to the standards and specifications that exist for approving antibiotics as an example of the kind of guidance they would like to see for all generic products: "We want to see the codification of specifications and required method of testing, as it exists for antibiotics. If we have to meet a certain standard of testing, tell us what the standard is in advance of our submission and work."

Even those respondents who viewed FDA guidance as adequate voiced concerns regarding FDA's inconsistency in *applying* the guidance. As one respondent said, "The guidance is

adequate, just inconsistent.... You've got a regulation that is three sentences long that says, 'You'll do it right,' and hundreds of people interpreting what that means." Another respondent who considers FDA guidance adequate added, "The regulations are pretty straightforward—but there are different requirements from different [FDA] divisions. Sometimes you wouldn't believe it's the same Agency."

For this reason, more respondents said that they rely primarily on previous experience in developing ANDAs (8) than regulations (3), guidelines (1), or discussions with FDA staff (3). Several respondents said that they review FDA comments made to previous submissions, evaluate those comments, and remember them in making their next submissions. These respondents added that they specifically tailor their submission to the division and reviewers assigned to the application. "Requirements vary from reviewer to reviewer," one respondent claimed. Another respondent said he said he considered guidelines irrelevant: "Ignore the guidelines and listen to what the individual chemist wants."

Respondents believe that communication between the Agency and industry is often inadequate, ineffective, or untimely.

Most manufacturers (10) felt it is difficult to find out the progress of review or the status of an ANDA. Respondents expressing this opinion were frustrated by their lack of access to reviewers as a result of the new FDA policy requiring applicants to contact Consumer Safety Officers (CSOs) rather than reviewers concerning their application. "It's turning into a bad scene; what used to be a relatively informal process [of calling reviewers directly] is now very formal [calling Consumer Safety Officers]." One respondent said, "We can't call reviewers, we can't meet with them....It's impossible to find out the status of a review. We're told, 'I can only tell you the review is in progress.' Consumer Safety Officers are hard to reach, don't return phone calls, and don't have a lot to say to us when they do."

Several respondents believed that communication has deteriorated in recent months. "In the past [communication] was spotty," said one respondent. "Now communication is nonexistent. It's like somebody put up a brick wall around the Agency." Another respondent echoed this sentiment: "[Finding out the status and progress of review] was very easy before the scandal. Now it is very difficult."

Most of the manufacturers we interviewed had not attended "end-of-review" conferences in connection with ANDAs, although several had done so in connection with NDAs. Many of the manufacturers were not aware that such meetings took place in connection with generic drug review. However, some of the manufacturers we interviewed had requested meetings with FDA at various stages in the review of their applications; one respondent thought these meetings were "granted reluctantly" and another who had requested numerous meetings said he often received the response, "Do you want a meeting or do you want an approval?"

Two manufacturers specifically expressed concern regarding their inability to obtain information from FDA on the “alert list,” which they described as a listing of manufacturers with outstanding deficiencies in manufacturing plants. According to these respondents, a manufacturer’s presence on the FDA’s “alert list” means that no ANDAs could be approved for that company until deficiencies were corrected. However, these officials maintained that companies on the “alert list” were not told they were on the list and given an opportunity to appeal the decision or move to quickly correct their deficiencies.

Respondents believe that FDA is inconsistent when reviewing ANDAs and making its decisions.

The lack of consistency in review was a foremost concern of many respondents. Twelve of the 16 respondents considered FDA review of applications inconsistent, citing differences between reviewers and divisions in the amount and nature of information they require and the importance they attach to various aspects of the application. Respondents sharing this opinion believed that inconsistency occurred due to a lack of standard operating procedures for reviewers to use in assessing ANDAs. “Different reviewers have different requirements, they emphasize different things,” said one respondent. “It becomes a game.” Another respondent thought that “you could submit the same file to two different reviewers and get two different decisions [based on their review]....Different decisions are made on different applications with the same data.” Some respondents blamed this inconsistency on poor management of reviewers. “FDA runs from the bottom up, not from the top down,” one respondent stated.

A majority of respondents (10) also believed that review of ANDAs was not well-planned. These respondents complained that they would receive a deficiency letter with certain problems identified and then receive subsequent deficiency letters listing more FDA concerns. These respondents were frustrated that all deficiencies were not identified sooner in the process. In addition, some respondents thought that FDA contradicted or repeated itself by asking the same question in one letter that it did in another; or by asking a question the manufacturer believed was obviously addressed in the application; or by asking for a change and later asking for another change back to the original position. In particular, manufacturers we interviewed pointed to chemistry review and labeling review as inconsistent and ill-planned.

Respondents believe that the Agency provides insufficient justification for decisions it makes on ANDAs.

Most respondents (11) have been dissatisfied with the decisions FDA has reached regarding the ANDAs they have submitted. Respondents expressing this view thought that “no justification was presented for decisions” or “the decisions are very close to being arbitrary and unreasonable.” Several respondents emphasized that they believe some FDA decisions on ANDAs lack scientific merit: “Small percentage differences can result in one application being approved and another [deemed] not approvable. Is [a certain percentage] good and [another percentage] bad? FDA can’t say.” Another respondent said, “We don’t argue with

[the justification], 'Science dictates you have to do this.' But that's not what we hear...[We hear], 'Because I said so.'"

Some respondents were also unclear about how policy decisions were made in FDA, or what constituted Agency policy. They are unhappy that "changes in policy are transmitted in an ANDA letter" where "we have no chance to comment on it." One respondent said, "FDA is implementing new requirements without input from industry, and some appear to lack scientific merit. When these requirements [are communicated], it is difficult to tell what represents Agency policy and what represents an individual reviewer's 'whim.' Nor is it easy to tell if the new requirement is the result of a passing conversation with an academician or an intensive 5-year study."

Respondents consider it difficult to appeal decisions made by the Agency on ANDAs.

Few respondents had ever formally complained to the Agency regarding the issues they discussed with us or concerning specific problems with specific ANDAs. These respondents had not done so primarily because they feared retaliation, believing "FDA has a long memory." One respondent who *had* made a complaint to the Agency had felt that his company paid a price: "While the submission was approved, it created future problems because of the resentment that somebody went over [the reviewers'] heads to the director." Other respondents who complained or appealed decisions were frustrated by the Agency's response. "The meeting [held] as a result of our complaint was not open but defensive," said one respondent. Another respondent said that his company had not "received a response up the ladder." Yet another official lamented, "There really is no true appeals process."

Respondents believe that there is inadequate staffing at FDA, or inefficient use of staff, to deal with the workload of ANDAs.

While respondents had varying opinions on the qualifications, competence, diligence, and fair-mindedness of FDA staff with whom they work on ANDAs, they pointed to a lack of resources or inefficient use of resources as reasons for a lack of timeliness and consistency in ANDA review. "They don't have enough people," one respondent said. "They need more clerical staff," thought another respondent.

Some respondents thought FDA could be more efficient in using its staff or organizing its review. Several respondents thought the Agency should take more advantage of field staff in conducting portions of the review: "They don't go to laboratories or plants as part of their review. They underutilize their field staff, one of their best assets, who have more hands-on experience." Another respondent who thought the review of ANDAs could be accomplished more efficiently by avoiding the duplication of work said: "FDA works hard but not smart. [We had] one experience where a reviewer approved one application with one drug master file. Then he moved to review our [application] next. Our application had the same drug master file, but the reviewer re-reviewed it all over again." Other respondents thought there should be more communication and interaction between the staff which reviewed the NDA for

the innovator product and the staff which reviews the applications for the generic equivalent, to create and share expertise on similar products; in fact, one respondent believed that FDA should co-locate the staff and make the same reviewers responsible for review of applications for both generic and innovator products of the same type. Finally, respondents again pointed to what they see as management problems: "There is no management control of FDA reviewers."

Respondents disagreed on whether two recent FDA initiatives, establishing of the Office of Generic Drugs and creating of an FDA ombudsman, would help address the concerns they discussed. Respondents did believe, however, that the FDA should continue sampling drugs on the market to ensure the quality of drugs sold to consumers.

Seven respondents believe creating an Office of Generic Drugs would be beneficial, three believed it would not help, and six were unsure. Those who thought such a move would be beneficial argued that "elevating [the office] gives it more prestige and attracts higher caliber employees." Those respondents who were unsure about the effect of the move thought that it might help if it resulted in more or better staff, but believed it would not address the main need for standard operating procedures or guidelines. The respondents who feel the new office will not meet their concerns considered it "window dressing."

Seven respondents believe creating an FDA ombudsman would be helpful, an equal number said it would not help, and two were unsure. One respondent who feels the creating such a position would help meet his concerns argued that an ombudsman could serve as a "pressure release valve between FDA industry," but stressed that autonomy was critical. Another respondent taking the view that an ombudsman would not help stated, "Unless you have an open door policy, the codification of specifications and requirements, an ombudsman is meaningless. What is he going to ombuds?"

Most respondents believe that FDA should test samples of marketed drugs, if only to reestablish consumer confidence in generic products. Several respondents emphasized the need for such testing to include innovator, or brand name, products.

Respondents suggested changes in FDA generic drug approval.

Some of the suggestions offered by respondents to improve FDA approval of generic products were to:

- *Develop more guidelines; codify and standardize specific requirements.* Some of the respondents expressing this view want to see detailed specifications for generic products, similar to those published now for approval of antibiotics. "When a drug is coming off patent," said one respondent, "publish requirements in the Federal Register and let manufacturers comment on them."

- *Develop standard operating procedures for reviewers.* Respondents recommending this change wish to address what they see as the inconsistency of review and decision making. Standard operating procedures would direct reviewers in how to assess ANDAs, what to look for during review, and what constitutes an approvable or not approvable ANDA.
- *Communicate more with industry.* Respondents suggesting this change desire more discussion of policy with industry as it is being developed, formal communication of policy to industry once it is adopted, more informal communication (e.g., telephone calls) with reviewers, availability of more information (e.g., alert list) to manufacturers, and development of a workable appeals process.
- *Increase FDA staff.* Respondents suggesting increased staff for ANDA review point to the increase in volume of submissions since 1984 and the need for the Agency to process submissions in a timely manner.
- *Reorganize review structure.* Some respondents suggested increased use of field staff to conduct portions of the review, such as validating production, equipment, and the conformity of the drug product with data in the ANDA. Another suggestion was to use the same reviewers to assess both NDAs and ANDAs for similar chemical compounds.
- *Pre-approve drug master files.* Several respondents thought that drug master files should be pre-approved, and simply referenced in the ANDA, rather than a drug master file reviewed and approved for each separate application.
- *Revisit supplemental requirements and review.* Some respondents suggested that FDA reconsider what changes merit a supplement or if such reviews could be contracted out. One respondent said, "If a facility change affects 10 applications, make 1 supplemental, not 10."
- *Standardize and streamline labeling requirements.* Some respondents thought that FDA should establish a "master" label for generic products. Others thought FDA should allow manufacturers to submit samples of labels to be marked up by reviewers, and then approve the label with changes to be incorporated in actual production.
- *Increase management control of reviewers.* Some respondents suggested that FDA should emphasize more the need for better supervision of reviewers, their quality of work and productivity, to reduce the variances and inconsistency in review.

- *Hold to time frames.* Respondents thought that minor deficiencies should not restart the review clock.

ENDNOTES

1. Except in those instances where a manufacturer has an approved suitability petition to seek approval of a product that differs from the listed drug.
2. Testimony of Dr. Frank E. Young, M.D., Ph.D., former Commissioner of Food and Drugs, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, on July 11, 1989.
3. Office of Inspector General, Office of Audit Services, "*Management Advisory Report: Vulnerabilities in the Food and Drug Administration's Generic Drug Approval Process*," A-15-89-00051, August 1989.
4. Fifteen manufacturers discussed their professional experiences with investigational new drug and new drug applications. For the results of these discussions, see Office of Inspector General, Office of Evaluation and Inspections, "*Perspectives of Drug Manufacturers: Investigational New Drug and New Drug Applications*," OEI-12-90-00771, February 1990.
5. See Food and Drug Administration, Office of the Commissioner, Office of Planning and Evaluation, "*Agency Impact Analysis: Fruit Juice, The Perceptions of Ten Firms*," OPE Study 70, June 1984, and "*Agency Impact Analysis: Salad Dressings, The Perceptions of Ten Firms*," OPE Study 64, May 1983.

APPENDIX A

LISTING OF PARTICIPANTS

- Abbott Laboratories
- Amersham Corporation
- American Cyanamid Company
- Barr Laboratories
- Biocraft Laboratories
- Bolar Pharmaceuticals
- Eli Lilly and Company
- G.D. Searle & Company
- Geneva Generics
- Hoechst-Roussel Pharmaceuticals, Inc.
- Hoffmann-La Roche, Inc.
- ICI Pharmaceuticals Group
- Lemmon Company
- Lyphomed, Inc.
- Merck Sharp & Dohme
- Mylan Laboratories
- Ortho Pharmaceutical Corporation
- Pfizer Incorporated
- Roxane Laboratories, Inc.
- Rugby Laboratories, Inc.
- Sandoz Corporation
- Schein Pharmaceutical, Inc.
- Schering-Plough Corporation
- Smith, Kline, & French

APPENDIX B

AGENCY COMMENTS



Memorandum

Date February 9, 1990
From Acting Commissioner of Food and Drugs
Subject OIG Research on Perceptions of Drug Approval Processes
To Inspector General

I want to thank your staff for sharing with FDA managers the recent OIG research into the perceptions of pharmaceutical executives regarding FDA's new drug and generic drug approval processes. In my prior FDA experience, I have always found opinions and observations expressed by parties affected by FDA to be a valuable source of feedback on agency performance.

FDA was particularly interested in industry perceptions about the drug approval processes last Fall, and I am pleased that your staff was able to collect this information for us so soon after Dr. Sullivan announced the various initiatives to strengthen FDA's drug review processes. This information gives FDA a very helpful insight as we proceed to strengthen these processes.

In addition to receiving the information itself, the process of sharing this information in a workshop setting with your staff was a positive experience. I look forward to more such interactions and exchanges between our staffs.


James S. Benson

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FEB 27 1990

Richard P. Kusserow
Inspector General

OIG Final Reports, "Perspectives of Drug Manufacturers: Abbreviated New Drug Applications," OEI-12-90-00770 and "Perspectives of Drug Manufacturers: Investigational New Drug and New Drug Applications," OEI-12-90-00771

James O. Mason, M.D.
Assistant Secretary
for Health

Attached for your information are the above-referenced reports, which discuss the findings from interviews conducted with officials at 24 drug manufacturing firms. This survey was conducted to assess the perspectives of industry in regard to new and generic drug approval in the Food and Drug Administration (FDA).

Respondents from 16 firms had experience with FDA's review of abbreviated new drug applications (ANDAs). Respondents from 15 firms had experience with FDA's review of investigational new drug exemptions (INDs) and new drug applications (NDAs).

FINDINGS

- o Virtually all the respondents we interviewed believe that FDA is effective in ensuring that only safe and effective drugs enter the market. The 15 respondents who discussed FDA's review of INDs and NDAs went on to say that they are generally satisfied with the decisions FDA reaches, the agency staff with whom they deal on their applications, and the communication between their firms and the agency.
- o The 16 respondents we interviewed concerning FDA's review of ANDAs were generally dissatisfied with the agency performance. They were critical of FDA's guidance, communication, and decision making.
- o Respondents in both categories identified inconsistency of FDA's review of applications as their primary concern. Respondents felt that the information required on an application, and the amount and nature of evidence on safety and effectiveness required by the agency, differ according to reviewer and division.
- o Respondents made a number of suggestions that they believe would improve agency performance if implemented. These suggestions are contained in the reports.

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Our staff discussed the findings and manufacturer recommendations contained in these reports with FDA officials in January 1990. The FDA provided us with technical comments to the reports, which we incorporated to clarify points made by the respondents, and a written response to the reports which we have attached.

Attachments

cc:

James S. Benson

Acting Commissioner of Food and Drugs

Prepared by:PThompson:BMTelesford:2-23-90