
PERSPECTIVES OF DRUG MANUFACTURERS

INVESTIGATIONAL NEW DRUG AND NEW DRUG APPLICATIONS



OFFICE OF INSPECTOR GENERAL
OFFICE OF EVALUATION AND INSPECTIONS

FEBRUARY 1990

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INVESTIGATIONAL NEW DRUG AND NEW DRUG APPLICATIONS

**Richard P. Kusserow
INSPECTOR GENERAL**

EXECUTIVE SUMMARY

PURPOSE

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

This report contains the accounts of manufacturers regarding their experiences and opinions of FDA's review of INDs and NDAs. 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 new drugs.

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 for use 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 their intended uses.

Investigational New Drug Application (IND)

To begin clinical studies on a drug product for human use, a sponsor (generally a pharmaceutical company or a research organization) must receive an exemption from FDA from the Act's provisions prohibiting distribution of new drugs not having approval from FDA. (21 U.S.C. 355(i).) To obtain this exemption, the sponsor supplies the FDA with a Investigational New Drug (IND) application containing all of the known information on the drug. This information is primarily data from studies conducted on animals, unless the drug has been used in Europe or elsewhere. Additionally, the sponsor must provide the FDA with detailed protocols, describing how the proposed human clinical trials will be conducted.

Generally, clinical trials are carried out in three phases. Phase 1 trials are conducted primarily to determine the safety of the drug and generally contain a small number of healthy volunteers, from 20 to 100. Phase 2 trials involve administering the drug to patients with the disease or condition for which the drug is intended to treat to determine whether the drug is effective. Phase 3 clinical trials are the most extensive of all, involving up to several thousand

patients. These trials provide information such as dosage rates and schedules that will allow the drug to be marketed and used safely and effectively.

New Drug Application (NDA)

A New Drug Application (NDA) is a sponsor's request to the FDA for approval to market a new drug. The NDA is the compilation of all of the clinical data regarding the safety and efficacy of the drug, as well as manufacturing information.

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 15 discussed their professional experiences with the IND and NDA review process. The results of those discussions are described in this report.¹

FINDINGS

All 15 manufacturers interviewed concerning FDA review of INDs and NDAs *consider the Agency effective in ensuring that drugs entering the marketplace are safe and effective.* Overall, respondents we interviewed concerning FDA's approval process for new drug products were less critical of the Agency than those we interviewed concerning FDA's approval for generic products.

For the following points, a majority of respondents

- *believe FDA provides adequate guidance to manufacturers on how to develop and submit successful INDs and NDAs;*
- *have found the IND rewrite useful;*
- *were generally satisfied with communication between their firms and FDA;*

- *are satisfied with FDA's decisions regarding IND and NDA submissions; and*
- *consider FDA staff qualified, competent, and fair-minded.*

Respondents are mixed regarding

- *whether FDA pays sufficient attention to the need for timely action on original NDAs. However, most respondents believe the agency pays insufficient attention to the need for timely action on supplemental NDAs.*

Respondents also believe

- *FDA review is inconsistent and ill-planned.*

Respondents suggested a number of changes to improve the IND and NDA approval processes.

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.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

INTRODUCTION	1
Purpose	1
Background	1
Methodology	4
FINDINGS	6
ENDNOTES	14
APPENDIX A	
LISTING OF PARTICIPANTS	A - 1
APPENDIX B	
AGENCY COMMENTS	B - 1

INTRODUCTION

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The FDA reviews the initial IND application requesting the exemption to determine if studies may proceed safely using human subjects. The FDA has 30 days in which to make its initial safety assessment and notify the sponsor of any concerns. After this time and if no safety concerns have arisen, the sponsor may proceed with clinical trials in humans. If FDA has safety concerns regarding the drug product at this time or at later points during clinical testing, it places a clinical hold on the trials. For later phases of drug testing, FDA may also place a

trial on clinical hold if the trial's design is inadequate to meet its stated objectives. Once FDA places a clinical hold, sponsors suspend clinical trials until the safety concern has been resolved to FDA's satisfaction.

Generally, clinical trials are carried out in three phases. Phase 1 trials are conducted primarily to determine the safety of the drug and generally contain a small number of healthy volunteers, from 20 to 100. Phase 2 trials involve administering the drug to patients with the disease or condition for which the drug is intended to treat to determine whether the drug is effective. Phase 3 clinical trials are the most extensive of all, involving up to several thousand patients. These trials provide information such as dosage rates and schedules that will allow the drug to be marketed and used safely and effectively.

When sponsors submit an application for an IND exemption to FDA, it must contain certain information. This information includes: (1) a cover sheet containing pertinent information about the sponsor, name of the investigational drug, and information on the Institutional Review Board and any contract research organizations; (2) table of contents; (3) introductory statement and general investigational plan; (4) investigator's brochure containing summaries of pharmacological and toxicological effects, pharmacokinetics and biological disposition, as well as human safety and effectiveness information and a description of risks; (5) protocols outlining each study; (6) chemistry, manufacturing, and control information; (7) pharmacology and toxicology information; (8) previous human experience with the drug; and (9) additional information on drug dependence and abuse potential of the drug. (21 CFR section 312.23.)

In 1987, regulations concerning the submission of INDs were revised. These new regulations are referred to as the "IND rewrite." The IND rewrite established deadlines for safety reports, encouraged meetings between FDA and the sponsor to discuss concerns, and allowed increased autonomy of sponsors in Phase 1 clinical trials. The IND rewrite also required sponsors to provide the FDA with an annual report which would, among other things, detail the plans for the drug's clinical development during the upcoming year and describe any safety problems that the sponsor has discovered.

The sponsor may meet with the FDA at certain points during clinical development. An "end-of-Phase 2" meeting takes place before large-scale testing in Phase 3 is begun. This meeting allows the FDA and the sponsor an opportunity to discuss data that will be required from the Phase 3 trials to complete the safety and efficacy profile of the drug. At the completion of Phase 3 trials and before filing the New Drug Application (NDA), the sponsor may also meet with the FDA. This is called the "pre-NDA" meeting. This meeting allows the FDA and the sponsor to discuss the nature and presentation of data to be included in the NDA.

New Drug Application (NDA)

A New Drug Application (NDA) is a sponsor's request to the FDA for approval to market a new drug. The NDA is the compilation of all of the clinical data regarding the safety and efficacy of the drug, as well as manufacturing information.

Specific information must be included in the NDA submitted by manufacturers to the FDA for approval to market a new drug. This information includes, among other things: (1) application form containing identifying data of the sponsor and drug; (2) index; (3) summary of submission containing proposed labeling, statement of intended use, description of marketing history, and risk/benefit analysis; (4) chemistry, manufacture, and control section; (5) nonclinical pharmacology and toxicology section; (6) human pharmacokinetics and bioavailability; (7) microbiology section (for anti-infective drugs); (8) clinical data section; (9) statistical section containing statistical evaluation of the clinical data; and (10) case report tabulations containing tabulations of data from Phase 1, 2, and 3 trials. (21 CFR 314.50.)

FDA classifies submissions according to the chemical type and most importantly, the treatment potential, to determine review priorities. According to FDA procedures, innovative compounds that are used to treat diseases and conditions for which there are no other treatments receive the first priority in review.

Once an application is submitted, FDA has 60 days to determine if the application may be filed. This means that FDA has made a threshold determination that the application is sufficiently complete to allow a substantive review. Once the application is filed, FDA then has 180 days to review an application and send the applicant either an "approval" 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 the review, communication takes place between FDA and the applicant. A "ninety-day conference" is offered to applicants approximately 90 days after the agency has received the application, during which FDA discusses with the applicant the status of the application, progress made to date in the review of the application, and deficiencies identified thus far in the review. An "end of review conference" is offered 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 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.

Regulations concerning NDA submissions were updated in 1985. These revised regulations are referred to as the "NDA Rewrite." The new regulations provided several additional safety features including safety reports after submitting the application and strengthened monitoring of adverse drug reactions from marketed drugs. The revision also facilitated review by requiring more focused and better organized data, use of summaries and tables, and allowance of approval on the basis of foreign studies alone.

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 15 discussed their professional experiences with the IND and NDA review process. The results of those discussions are described in this report.¹

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.²

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 survey 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

All 15 manufacturers interviewed concerning FDA review of INDs and NDAs *consider the Agency effective in ensuring that drugs entering the marketplace are safe and effective.* Overall, respondents we interviewed concerning FDA's approval process for new drug products were less critical of the Agency than those we interviewed concerning FDA's approval for generic products.

For the following points, a majority of respondents

- *believe FDA provides adequate guidance to manufacturers on how to develop and submit successful INDs and NDAs;*
- *have found the IND rewrite useful;*
- *were generally satisfied with communication between their firms and FDA;*
- *are satisfied with FDA's decisions regarding IND and NDA submissions; and*
- *consider FDA staff qualified, competent, and fair-minded.*

Respondents are mixed regarding

- *whether FDA pays sufficient attention to the need for timely action on original NDAs. However, most respondents believe the agency pays insufficient attention to the need for timely action on supplemental NDAs.*

Respondents also believe

- *FDA review is inconsistent and ill-planned.*

Respondents suggested a number of changes to improve the IND and NDA approval processes.

Each of the findings is discussed in more detail below.

All manufacturers interviewed regarding new drug approval believe FDA is effective in ensuring that drugs entering the marketplace are safe and effective.

All 15 respondents interviewed concerning IND and NDA review feel FDA does an effective job in ensuring that drugs entering the market are safe and effective. One respondent who rated the agency as very effective, added, "They [FDA] have fulfilled their charter well; in fact your scale is not high enough in this regard." Several manufacturers observed that FDA is highly regarded worldwide for its safety standards.

The majority of respondents believe the Agency provides adequate guidance to manufacturers on how to develop and submit successful INDs and NDAs.

The majority of respondents (11) rated the guidance from the FDA in preparing the original IND as adequate or more than adequate. Guidance relied on by manufacturers to develop their INDs includes discussions with FDA staff, regulations, and guidelines. "The guidance is adequate," said one respondent. "[We get it] both verbally and through documentation."

Several respondents believe that FDA should attempt to update guidelines for clinical development, which they considered to be out of date. For example, one respondent who considered FDA guidance on developing an IND submission adequate added, "While the guidelines are clear, they're old..." Another respondent who considered agency guidance inadequate pointed to this as the reason: "Clinical guidelines have not been updated in almost 13 years."

Most respondents (13) also feel information provided by the agency on how to prepare and submit NDAs is adequate or more than adequate. Again, guidance relied on by manufacturers to develop their NDAs includes discussions with FDA staff, regulations, and guidelines.

Most respondents have found the IND rewrite useful.

The majority of respondents (9) reported that the 1987 rewrite has been very or moderately useful to them in preparing successful IND submissions. Five respondents consider the new regulations of little use; one respondent was unsure. "It codified a lot of the process that people had previously guessed at based on past experience," said one respondent. Another respondent added, "It helped a lot; [FDA] really took the best practices of many companies and combined this in the regulation. One company does [one thing] really well, so FDA decided that everyone should adhere to that practice; one company does [another thing] really well, so FDA decided that everyone should adhere to that practice; and so on."

Overall, respondents indicated that the rewrite has resulted in more work for sponsors since more information must be submitted. Most of the manufacturers indicated they had no problem with supplying the FDA with more information if it helped the reviewers. However, several respondents wondered whether the additional information, especially the annual report, was being reviewed at FDA or simply filed.

Some manufacturers believe that the use of clinical holds has increased since the implementation of the IND rewrite. One respondent indicated that the 30-day review period is not allowing reviewers the time they feel they need to perform a safety review, causing them to be overly cautious. He explained, "The regulations themselves are very good...[but] FDA does not seem to fully follow the intent of the regulations. The problem of clinical holds has become a bigger problem since the IND rewrite. Since they only have 30 days, sometimes you get a 'knee-jerk' reaction if they have any question at all."

Respondents were generally satisfied with communication between their firms and FDA. However, they emphasized that communication must be timely and accurate in conveying the agency's position in order to be most useful.

Checking on the status of applications. Two-thirds of the respondents (10) considered it fairly easy to check on the progress of an IND submission. Respondents indicated that Consumer Safety Officers (CSOs) are generally eager to help and provide status reports. Slightly more than one-half of the respondents (8) considered it fairly easy to find out the progress of a NDA submission and its status. A few respondents (2) thought checking on NDA status was difficult and several (3) indicated it varies from division to division.

Communicating with FDA during clinical trials. Almost all of the respondents indicated that they had attended the various meetings made available by FDA during the IND phase. The majority of respondents rated these meetings, which include the "End of Phase 2" and "Pre-NDA" meetings, as very useful and generally indicated that they would take advantage of any opportunity presented to meet with reviewers. "You would be out of your mind not to sit down with reviewers and discuss the submission when given the opportunity," said one respondent.

Respondents did note, however, that conclusions reached in "End of Phase 2" and "Pre-NDA" meetings could not always be considered final. "[You] can have a well-documented meeting but because division directors aren't present, FDA doesn't feel obligated to adhere to agreements," one manufacturer said. "Sometimes you need to have certain individuals present to know that meeting results will fly."

Virtually all manufacturers had sought advice from FDA during the course of clinical trials and found that advice useful. However, timeliness is crucial to sponsors, especially when changes and additions are needed in clinical protocols and studies during the IND phase. Several respondents related incidents where FDA had contacted them with changes in the design of clinical trials only to find out the trial had already been completed.

Communicating with FDA during NDA review. Nine respondents had attended a "ninety-day conference" and 10 had attended an "end-of-review conference".

Respondents who had attended a "ninety-day conference" were split on their usefulness. According to several manufacturers, FDA frequently has not had sufficient time to even begin the review at the time of the "ninety-day conference". Some respondents thought that, for this reason, FDA often will not grant requests for these meetings. "We attended one 'ninety-day conference' and found it very useful, said one manufacturer. "But we have...requested numerous other ['ninety-day conferences']. These did not take place because FDA said, 'We have nothing to talk about'."

Nine of the 10 respondents who had attended an "end-of-review conference" found them useful. At these meetings, manufacturers discussed with FDA continued testing for adverse drug reactions, final labeling, and other issues of interest.

Respondents are generally satisfied with the Agency's decisions regarding IND and NDA submissions.

The majority of respondents (13) were satisfied with the final decisions made by the FDA regarding their IND submissions. Many manufacturers pointed out their concerns are with how FDA reaches their decisions, not what decisions are made. One respondent described himself as "ultimately satisfied with decisions, but frustrated along the way." Another respondent stated, "Decisions are always justifiable and based on some sound principles of science." However, this same respondent went on to point out that "what is missing is the discussion between industry and FDA on those scientific questions."

Several respondents expressed frustration with clinical holds. One manufacturer stated, "There have been open-ended delays with clinical holds. FDA does not have a sense of urgency to remove clinical holds...during the course of an IND [phase], we can have formal and informal clinical holds. With informal clinical holds, we can have questions on a minor part of the protocol disrupt the program." Several manufacturers mentioned that they believe FDA is aware of the problem with "informal" clinical holds and is moving to address it.

The majority of respondents (12) expressed similar satisfaction with the decisions made by FDA regarding NDA submissions. Again, however, many of the respondents would like to see decisions reached more quickly on NDA submissions. One respondent stated, "[It] just takes them longer to reach the same decision [that we would have]."

Respondents consider FDA staff qualified, competent, and fair-minded.

The majority of the respondents consider the FDA staff with whom they work to be qualified (11), competent (8), and fair-minded (12). Several respondents believe that these qualities vary significantly from employee to employee.

Several respondents mentioned several factors they feel affects the ability of FDA staff to carry out their function, such as less than desirable working conditions, relatively low pay, and

insufficient staffing. One respondent felt that the FDA staff “get a bum rap” and that “taxpayers are getting a good deal for their money.” One respondent commented that the working conditions were bad and he “probably couldn’t do a better job.”

Another respondent felt that the work system at FDA does not reward industriousness: “[There are] no rewards in FDA for working hard and good. There are only penalties for getting a drug out if anything goes wrong. If a reviewer works rapidly, they just get another assignment.”

Respondents have mixed opinions on whether the Agency pays sufficient attention to the need for timely action on original NDAs. However, most respondents believe the agency pays insufficient attention to the need for timely action on supplemental NDAs.

A slight majority of respondents (8) believe that FDA is ineffective in ensuring that drugs enter the marketplace in a timely manner. However, almost as many (7) thought FDA is effective in getting applications processed in a timely manner. One respondent who considers FDA ineffective argued, “After five months they know [the drug] is safe and effective; the rest is unnecessary details, bureaucracy, and poor management.” A few respondents thought FDA is too cautious in its review, expressing the opinion that FDA “goes overboard” in ensuring safety and over-emphasizing the risk side of the risk/benefit relationship. Another respondent disagreed, rating the agency as effective in ensuring the timely movement of drugs to market and arguing that delays were generally the fault of industry: “The overwhelming factor that usually influences review time is the quality of the data sent to FDA.”

All of the manufacturers interviewed had submitted at least one supplemental NDA. The majority (11) believed that supplementals were reviewed less expeditiously and received a lower priority than NDAs. Several manufacturers expressed frustration with this situation saying that FDA had directed them to streamline original NDAs and pursue additional indications later in supplemental NDAs. The manufacturers we interviewed said that they understand that new drug approvals are the top priority at FDA, but they pointed out that expanded indications from already marketed drugs provides companies with revenue for research and development.

Respondents disagreed on whether FDA is effective in establishing review priorities in order to expeditiously review certain applications. Most manufacturers agreed that except in the case of 1-AA compounds, such as those to treat AIDS, the classification a drug receives has little bearing on review time. “The difference between a priority NDA and a nonpriority NDA in terms of average review time to approvable is only about three months,” declared one respondent.

Respondents believe that FDA review is inconsistent and ill-planned.

The majority of respondents consider FDA review of NDAs inconsistent (12) and FDA review of INDs inconsistent (13). Respondents characterized the review process as highly variable

from division to division and from reviewer to reviewer in a given division. Respondents attributed the variability to lack of guidelines and standard operating procedures for reviewers, as well as individual differences in background, interest, and dedication. One manufacturer reported, "We have cases in which the same set of data used to support 10 approved NDAs is suddenly found to be deficient by a reviewer in another division."

Several manufacturers believed that the worst scenario is having a change of reviewers during the course of the IND and NDA submission. According to respondents what was accepted and agreed upon for clinical studies may no longer be acceptable with a new reviewer. Inconsistency among divisions is especially apparent when a reviewer switches to a new division and tries to apply the standards of the former division to the review process. Respondents also pointed out that divisions use their advisory committees in differing capacities which results in differences in some management practices.

The majority of respondents (9) also considered the review of INDs ill-planned. Respondents' concerns about the lack of planning in the process focused on identifying deficiencies late in the review process, asking inappropriate questions early in the clinical development, and lacking on-going review of clinical information in the IND phase. One manufacturer stated, "you proceed until you hear; but this often causes delays because you have not been informed early on." Another manufacturer noted, "[Review of] the original IND is well-planned, but the entire process is not. Throughout the process, we are not sure that anybody is looking at the data we send in. FDA is inundated with paper and has no time to pull the entire IND and reflect on it as a whole. We get to a pre-NDA meeting and find out that we are supposed to redo a toxicology study we did five years ago. FDA has had the data for five years; why are we just finding out about their concerns?"

Comments were similar concerning the NDA process, with 10 respondents feeling that the review process is ill-planned. Several manufacturers reported the same experience: receiving questions from reviewers that are addressed in the submission, to which the manufacturer replies, "See page 4, paragraph 2, of our submission"; and receiving new questions after an initial letter stating the application's deficiencies have been received by the manufacturer and addressed.

Respondents suggested a number of changes to improve the IND and NDA approval processes for innovator drugs.

- *Overall, respondents would like to see a less adversarial relationship with FDA.* Several respondents indicated they feel FDA views their role as a policing job instead of a regulatory agency. Manufacturers would like to see an agency-industry "partnership" in getting new drugs to the market.
- *More feedback to industry on protocols and submissions during the IND phase.* The majority of the manufacturers interviewed would like to have more input

from FDA on the design of clinical trials. Respondents feel FDA should be willing to look to the future and be more specific of what they will require of future studies.

- *Update guidelines.* Respondents would like to see guidelines updated, especially those relating to clinical trials.
- *Earlier—or later—involvement by FDA in the IND process.* Some of the respondents would like to see FDA involved in the overall clinical development of the drug at an earlier point. These manufacturers would like more security that the development course they are following is one that FDA approves of. An equal number of manufacturers would like to see the IND phase deregulated, with less FDA involvement. These respondents feel that liability concerns are sufficient to ensure that safety issues are adequately addressed. Some manufacturers would also like to see detailed product formulation data and manufacturing information requested at a later point in time, not in the initial IND.
- *Complete review of data as it is submitted during the IND phase.* Respondents would like to see review of the NDA become more of a final formality in the review process. Manufacturers pointed out that generally the information submitted in the NDA has already been sent to the FDA and many times has already been approved once. Respondents feel that too much time is spent re-reviewing data.
- *Develop standard operating procedures for review.* Respondents would like to see more consistency from reviewer to reviewer and among different divisions. Manufacturers suggested developing standard operating procedures and guidelines for reviewers to reduce inconsistency.
- *Hold to review clocks.* Manufacturers acknowledged it would be difficult for FDA to complete NDA reviews within the current 180-day time frame. They would like to see more realistic time frames established and have FDA stay within them. Several manufacturers felt that reviewers did not feel bound by the current 180-day period because the time frame is so unrealistic.
- *Clarify regulations and role of foreign data.* Manufacturers would like to see a more accepting attitude from FDA towards foreign data. Several respondents indicated they would like to see further clarification in the regulations specifying exactly how much of the foreign data needs to be submitted and will be accepted by FDA.

- *Change the way supplemental NDAs are handled.* Manufacturers would like to see more timely review of supplemental NDAs. They suggested the review time could be shortened by having the reviewer of the original NDA handle all supplements for that drug. This would prevent another reviewer from losing significant time reviewing the original NDA prior to looking at any supplements.
- *Improve management.* Respondents would like to see some changes in the management structure at FDA. It was a frequently expressed opinion that divisional directors were being asked to do too much in trying to be both scientist and manager. Respondents also felt that managers rarely contradict or override the decisions of the reviewers under them and are afraid to do so. Respondents would like to see more managerial control over individual reviewers.
- *Increase staffing.* Several manufacturers expressed the feeling that even if all management and procedural concerns could be resolved, insufficient personnel would still prevent FDA from being able to ensure timely approval of new drugs.
- *Better understanding of pharmaceutical manufacturing issues.* Respondents suggested exchange programs with the industry as a method for FDA staff to become more familiar with the pharmaceutical manufacturing process.

ENDNOTES

1. Sixteen manufacturers discussed their professional experiences with FDA review of abbreviated new drug applications. For the results of these discussions, see Office of Inspector General, Office of Evaluation and Inspections, "*Perspectives of Drug Manufacturers: Abbreviated New Drug Applications*," OEI-12-90-00770, February 1990.
2. 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



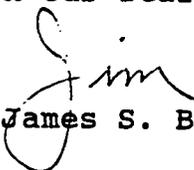
Memorandum

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

