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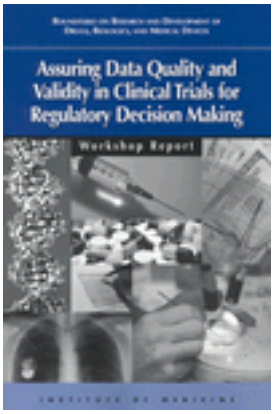

Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: Workshop Report

Jonathan R. Davis, Vivian P. Nolan, Janet Woodcock, and Ronald W. Estabrook, Editors; Roundtable on Research and Development of Drugs, Biologics, and Medical Devices, Institute of Medicine

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THE NATIONAL ACADEMIES
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Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making

Workshop Report

Roundtable on Research and Development of
Drugs, Biologics, and Medical Devices

Jonathan R. Davis, Vivian P. Nolan, Janet Woodcock, and
Ronald W. Estabrook, *Editors*

Division of Health Sciences Policy

INSTITUTE OF MEDICINE

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The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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ROUNDTABLE ON RESEARCH AND DEVELOPMENT OF DRUGS, BIOLOGICS, AND MEDICAL DEVICES

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Preface

THE ROUNDTABLE

The Institute of Medicine's (IOM's) Roundtable on Research and Development of Drugs, Biologics, and Medical Devices evolved from the Forum on Drug Development, which was established in 1986. The importance of maintaining a neutral setting for discussions regarding long-term and politically sensitive issues was determined by sponsor representatives and the IOM to justify the need to revise and enhance past efforts. The new Roundtable is intended to be a mechanism to convene a broad group of experts to conduct a dialogue and exchange information. The experts consist of individuals, including government officials (who serve in an *ex officio* capacity), who represent all sides of public policy issues related to the development of drugs, biologics, and medical devices.

Members of the Roundtable bring expertise from areas of clinical medicine, pharmacology, health policy, health insurance, industrial management, and product development as they pertain to research and development of drugs, biologics, and medical devices. Each member's participation adds a unique perspective to discussion topics. Members are responsible for identifying areas of Roundtable focus and determining issues that can be further elucidated in subsequent workshops. These workshops provide the opportunity to assemble a broader group of experts in the area of interest.

The goals of the Roundtable include the provision of an environment for the exchange of information and the identification of high-priority issues in the areas of product discovery and development. To achieve these goals the Roundtable convenes twice annually and holds at least one workshop annually.

The Roundtable identifies opportunities and problems that are current and likely to be ongoing, or that are expected to arise within the next few years and develops approaches to exploiting opportunities or solving problems. Several issues that have been suggested by Roundtable members as possible discussion topics are listed below:

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- medical devices,
- genomics and gene therapy,
- product development for special populations, and
- public education and risk assessment.

To allow full and candid participation by all members, reports of Roundtable discussions and workshops identify approaches but do not make recommendations or endorse specific courses of action.

WORKSHOP REPORT AND ITS ORGANIZATION

In an effort to increase knowledge and understanding of the process of assuring data quality and validity in clinical trials, the IOM hosted a workshop to open a dialogue on the process to identify and discuss issues of mutual concern among industry, regulators, payers, and consumers. The presenters and panelists together developed strategies that could be used to address the issues that were identified. This IOM report of the workshop summarizes the present status and highlights possible strategies for making improvements to the education of interested and affected parties as well as facilitating future planning.

This report is divided into two major sections: (1) presubmission and submission of clinical data and (2) regulatory review of these data by the Food and Drug Administration (Food and Drug Administration). The content of the presubmission of clinical data is derived from discussions of the actions frequently undertaken by representatives of the pharmaceutical and clinical research industries. These individuals gave presentations on data collection, which addressed such issues as documentation, investigator selection and training, data complexity, and the number of clinical trials conducted; monitoring, which addressed such issues as common practices of the industry and auditing by third parties; and data handling and cleanup, which addressed such issues as common practices of the industry, costs and time required for data handling and cleanup, and troubleshooting.

The first section also addresses submission of clinical data to the FDA. Here, the issues addressed were specifically concerned with the preparations of marketing applications, such as similarities and differences in content requirements, time and cost estimates, and validation considerations.

The second section on FDA regulatory review was based on presentations by representatives from the FDA. These presenters discussed paper auditing, clinical site review, and institutional review board auditing. They also addressed integrity assessments, common patterns and practices, and sanctions for noncompliance.

The basic tenets of the workshop were exploration of reasonable standards that will result in better quality data without inflation of the process costs and that will assure that these standards result in accurate and reliable data. The following themes were addressed during the 2-day workshop:

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• What are the benefits of assuring the quality of clinical data? Are they commensurate with the costs? What are the implications for cost and timing of clinical development? What are reasonable standards for data quality, and how could such standards be developed? How should adequate quality be defined?

• How much is considered enough data?

• How do other countries assure quality of clinical data?

• How can the system or process be improved (i.e., streamlining of data collection and maintenance of quality?

• How will automation of data collection, central monitoring, and remote data entry affect quality?

• How does austerity affect the management of clinical research programs? How will managed care and third-party payment policies affect these programs?

The agenda for the workshop is included in Appendix A of this report. The main body of the report follows the agenda's general outline and is largely based on a verbatim transcript of the workshop. However, explanatory material has been added to the introduction, and moderator's summaries have been combined and streamlined for greater clarity.

The report is organized as a topic-by-topic synthesis of exchanges during the workshop. The names of the individuals who made presentations on individual topics are identified for each section. These individuals have reviewed and approved the sections for accuracy. All Roundtable members have also had the opportunity to review the document, and those present at the workshop have indicated that the report accurately reflects the workshop discussions.

The Roundtable asks the reader to remember that any single workshop is necessarily incomplete and that its proceedings can report only on what participants stated at the workshop. Therefore, this report cannot serve as an exhaustive exploration of its subject matter since the information reported in the text emerged in the workshop itself.

At the same time that this report provides an account of individual presentations at the workshop, the dynamics of the Roundtable are such that the report also reflects a very important aspect of the Roundtable philosophy. That is, this report reflects the Roundtable's function as a convenor of representatives from different sectors for dialogue and their thoughts on which subject areas and research may merit further attention. However, the reader should understand that the material presented here expresses the views and opinions of those participating in the workshop and not the deliberations of a formally constituted IOM study committee.

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Acknowledgments

On behalf of the Roundtable and the Institute of Medicine (IOM), warmest appreciation is expressed to the individuals and organizations who gave valuable time to provide information and advice to the Roundtable through participation in the workshop. Each of the following contributed greatly: Susan Alpert, Food and Drug Administration (FDA); Robert Califf, Duke Clinical Research Institute; Michaele Christian, National Institutes of Health; Michael Clayman, Eli Lilly & Company; Susan Ellenberg, FDA; Ronald Estabrook, University of Texas, Southwestern Medical Center at Dallas; William Fairweather, FDA; Frank Hurley, Quintiles Transnational Corporation; Charma Konnor, FDA; Kiyoshi Kuromiya, Critical Path AIDS Project; David Lepay, FDA; Robert Levy, American Home Products, Wyeth-Ayerst Research; Murray Lumpkin, FDA; Michael McGarvey, Blue Cross and Blue Shield of New Jersey, Inc.; Royer Meyer, American Association of Medical Colleges; Kristin O'Connor, Boehringer Ingleheim Pharmaceuticals; Nicholas Pelliccione, Schering Plough; Jim Phillips, Quintiles Transnational Corporation; John Schultz, Neuroclinical Trials Center, University of Virginia; Eleanor Segal, Chiron Corporation; Kenneth Shine, IOM; Jay Siegel, FDA; Whaijen Soo, Hoffmann-La Roche, Inc.; Frances Visco, National Breast Cancer Coalition; William Waggoner, Essex Institution Review Board; Janet Woodcock, FDA; and Stan Woollen, FDA. The other workshop attendees who also deserve special recognition participated as guests. These individuals are identified in Appendix C. All the workshop participants played an important part in this activity, especially in stimulating discussion and providing ideas.

The Roundtable also wishes to thank the following individuals who participated in the workshop's organizing committee and working group and who contributed greatly to ensure the success of the workshop: Leslie Benet, Jim Benson, Bruce Burlington, Robert Levy, Paul Rogers, Daniel Seckinger,

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Whaijen Soo, Janet Woodcock, and Kathryn Zoon. Additionally, the Roundtable especially thanks Matthew J. Tarosky, Program Management Officer at FDA's Center for Drug Evaluation and Research, for assisting with the planning of the workshop and for providing assistance with the Glossary and Acronyms, which can be found in Appendix D.

The Roundtable expresses much appreciation to the IOM staff who provided invaluable help in this activity. Andrew Pope directed the Roundtable at its inception and was instrumental in planning and organizing this workshop. Christina Thacker assisted with the workshop planning and logistics. Of particular note, Nicole Amado developed the Glossary and Acronyms list and provided comprehensive administrative support to facilitate the development of the report. During report review, Sue Barron, Claudia Carl, and Mike Edington provided valuable direction and technical assistance.

Other professional staff also provided invaluable help. Paul Phelps, an independent writer, incorporated into the first draft the many pieces of written material presented during the workshop. The extensive commentary and suggestions made by the copy editor, Michael Hayes, are gratefully acknowledged.

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This report has been reviewed by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the Institute of Medicine in making the published report as sound as possible and ensuring that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The contents of the review comments and the draft manuscript remain confidential to protect the integrity of the deliberative process. The Roundtable and IOM wish to thank the following individuals for their participation in the review process: Margaret Anderson, Society for the Advancement of Women's Health Research; Daniel L. Azarnoff, M.D., D.L. Azarnoff Associates; John J. Burns, Ph.D., Cornell University Medical College; Farley Cleghorn, Ph.D., University of Maryland; and Myron M. Levine, M.D., University of Maryland School of Medicine.

Although these individuals provided many constructive comments and suggestions, responsibility for the final content of this report rests solely with the authoring committee and the Institute of Medicine.

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Executive Summary

The goal of improving health through the use of new medicines and medical devices cannot be achieved without public confidence and participation in the clinical trials process. During clinical development, investigational therapies are tested with human subjects, yielding essential information for assessments of their safety and effectiveness. The importance of informed consent and human subject protection to the integrity of the clinical trials process has been widely discussed over the last 50 years. It is well accepted that human subjects should not be needlessly exposed to risks in trials that fail to yield valid data. Assuring the quality and therefore the usefulness of the data from human clinical trials, however, has received less attention, but it is also a crucial topic because public confidence in the value of clinical trials is ensured when the public knows that the data are of high quality and useful. In addition, regulatory and medical decisions about approval or use of new or novel therapies are dependent upon the reliability of data from clinical trials. For these reasons, there is widespread agreement that data from such trials should be of high quality.

Despite this fundamental agreement, many challenges remain. The current processes for assuring data quality were developed individually in response to various problems or crises rather than in a comprehensive quality management framework. Although the current system is successful, it is relatively expensive and time-intensive, may limit the overall investment in clinical trials, and may not provide the best-attainable quality for the degree of investment. Additionally, there is no consensus definition of "quality" as it applies to data from clinical trials. Finally, many changes that have the potential to affect data quality are occurring in the areas of clinical practice and clinical trials, including widespread computerization of data entry and handling, use of contract research organizations (CROs) to perform or organize clinical trials, the increased frequency of multinational trials, and changes in the health care delivery system.

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The Roundtable on Research and Development of Drugs, Biologics, and Medical Devices convened a workshop on April 14 and 15, 1998, to discuss these and related topics. Representatives of major parties with vested interests in new medical product development were included. The workshop was successful in broadening the dialogue among the Food and Drug Administration (FDA), industry, and the public on the subject of data quality and validity in clinical trials for the regulatory decision-making process. The workshop participants described the components of the current system, and debated challenges and opportunities for improvement.

ASSURING CLINICAL TRIAL DATA VALIDITY: THE CURRENT PROCESS

Data quality efforts begin during the planning stages of a clinical trial and continue throughout FDA review of a marketing application. Product developers are responsible for planning and conducting trials, assembling and analyzing data, and preparing accurate regulatory submissions. FDA recently published the *Guidance for Industry on Good Clinical Practices*. This document, which represents a harmonized position among the regulatory bodies of the United States, the European Union, and Japan, provides advice on record keeping and procedures for many aspects of the conduct of clinical trials. After receiving an application, FDA evaluates the quality of the data that have been submitted, and also performs audits at clinical trial sites to further assess data quality. The following sections describe the major components of these processes.

Design of Protocol, Case Report Forms, and Data Collection Systems

The industry, government sponsor, or a CRO prepares the clinical protocol, including the forms used for collection of clinical data (often with input from FDA). The organization also develops computer systems for creation of a database and analysis of the information. The protocol and the case report form design, particularly the complexity of the design and the amount of data collected, have important influences on data quality. Some companies are now using remote data entry systems, whereby some or all trial data are entered directly into a computer or a centralized database. The designs of such systems present challenges to regulators.

Clinical Investigator and Study Personnel Training

The sponsor or a CRO trains physicians who will be conducting the study and trains study coordinators and other personnel who organize the study at each

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site. This training is critical to ensuring that the protocol is followed correctly and that case report forms are properly completed.

Clinical Site Monitoring

The sponsor or a CRO periodically sends trained personnel (monitors) to each study site to check on the progress and quality of performance of the study. Monitors review case report forms and other study records to ensure that the documentation is complete. The pharmaceutical industry estimates that the monitoring of drug trials can consume 15 to 30 percent of overall trial costs.

Industry Data Quality Assurance Procedures

This step involves assembly of all the data from the trial, entry of the information into databases, and evaluation of the data for quality. If case report forms are paper-based, double data entry into the database is usually performed to minimize transcription errors. The data are then subjected to extensive quality assurance procedures involving follow-up activities on missing or potentially inaccurate datum points. Often, audits of clinical sites will be performed by the sponsor or a CRO as part of the industry quality assurance program.

FDA Data Analysis

FDA clinical reviewers and statisticians evaluate the data submitted in the application. FDA data analysis often includes checking and verification of data from important analyses submitted by the sponsor, as well as performance of exploratory analyses to answer questions that emerge from the review.

FDA Data Quality Assurance Evaluation

FDA clinical reviewers evaluate the quality of the data in the application using techniques such as auditing of case report forms to verify the accuracy of tabulated data, evaluation of follow-ups on reported adverse events, and verification of the primary outcome measure at the case report form level. An overall assessment of data quality is developed. The overall assessment is a factor in determining whether the application merits approval. If serious questions regarding overall data integrity are not resolved, FDA will not approve the application.

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FDA Clinical Study Audit Program

During application review, FDA selects clinical sites that generated data for the application for auditing purposes. A thorough on-site review of these sites is conducted by trained FDA inspectors. Record keeping, adherence to the protocol, informed-consent procedures, and other aspects of the study are assessed. If objectionable conditions are found, a report (referred to as FDA Form 483) is provided to the principal investigator at the conclusion of the audit.

FDA Enforcement Activities

If an investigator is found to have serious or repeated problems in performing clinical studies, FDA will take steps to debar the individual from performing trials for regulatory purposes. In cases of fraud, criminal prosecution may be pursued.

OPPORTUNITIES FOR IMPROVING THE PROCESS

During the workshop participants identified a number of opportunities for significant improvements in the overall process. Some of the goals included the need for an increase in the dialogue among the involved parties, maintenance or improvement of quality with a concomitant lowering of costs, increases in the levels of public knowledge and confidence in the process, a means of dealing with emerging changes such as widespread computerization and delivery of new therapies to the market, and protection of the public from risk. Overall, participants identified a need for systemic collaborative improvements, such as improving processes in the context of the entire system with the input of all parties involved in the system. The following sections describe some of the targeted and overall strategies for improving the process.

Targeted Strategies

Broader Involvement of Patient and Consumer Groups

• Representatives of patient and consumer groups indicated that extensive involvement of their constituencies was essential to ensure that their needs and concerns are accounted for and adequately addressed. The constituencies' confidence and participation in the clinical trials process is essential to successful product development.

• Additionally, particular concerns of patient representatives included issues of conflict of interest and investigator bias. Reimbursement of investigators for recruitment and retention of trial subjects was an issue; this practice could be

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a disincentive to maintaining high quality in clinical trials. The interrelated aspects of financial reimbursement and incentives, as well as scientific conduct in clinical trials, deserve further discussion.

Greater Emphasis on Building Quality into the Process

In the current system, both industry and FDA expend considerable effort auditing and correcting data once the data are collected. Many participants suggested that higher quality could be achieved by designing quality during the planning stages of clinical programs.

Overall Strategies

The following sections describe some of the opportunities for improving the overall process of assuring data quality and validity.

More Extensive Training of Clinical Investigators and Study Personnel

Since many quality problems result from failure to follow study designs, protocols, or collect data properly, development of a larger cadre of well-trained and experienced investigators and study personnel has the potential to improve data quality across studies. Many organizations are now interested in providing or participating in such training.

Data Standardization

Standardization has been successfully used in many industries to improve quality. In the clinical trial arena, terminologies, forms or computer screens used to collect data, and the tools and systems used to analyze the data are candidates for standardization. Entries for medical events and for concomitant medications were noted as areas of particular complexity. FDA is evaluating ways to further standardize the presentation of safety data.

Data Simplification

Although millions of data points are collected during the average clinical trial, some of these data are not used in the decision-making process. One important strategy for improving quality is to simplify data collection by distinguishing critical data prospectively. Further work is needed to provide a better understanding of what data sets are being submitted and how they might be simplified.

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Improvements In Quality Control and Quality Assurance Methods

Benchmark standards are developed for data quality in the clinical trial setting. A significant amount of effort goes into detecting and correcting problems, such as missing data points and transcription errors, which are very different from uncertainty issues. Participants agreed that there is a "hierarchy of errors." Because a clinical trial often generates millions of data points, ensuring 100 percent completeness, for example, is often not possible; however, it is also not necessary. High-quality data may be defined as data strong enough to support conclusions and interpretations equivalent to those derived from error-free data. Certain data points are more important to interpreting the outcome of a study than others, and these should receive the greatest effort and focus. Implementation of this definition would require agreement on data standards.

Evaluations of monitoring and auditing techniques are also needed. Industry uses a variety of monitoring and auditing techniques to ensure high-quality data. These have not been compared or tested to see which are the most effective. Additional discussions and evaluation of monitoring and auditing techniques should be undertaken.

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Introduction

THE TOPIC

The development of a new drug is a challenging and time-consuming process. If preclinical testing suggests that a promising compound might be well tolerated in humans, it is tested for safety and pharmacokinetics in healthy volunteers (Phase 1). If the results of Phase 1 trials warrant further investigation, a limited number of patients with the target disease are challenged with the drug under carefully controlled conditions to evaluate its efficacy and further establish safety and proper dosages (Phase 2). If these trials are successful, the drug enters large-scale trials to better characterize its safety and efficacy in patients (Phase 3). Typically, clinical trials are coordinated by either contract research organizations (CROs) or academic medical centers that are sponsored by the pharmaceutical manufacturer. Physicians at these institutions conduct the clinical trials and care for the patients. The Food and Drug Administration (FDA) is the regulatory body involved during the development, preclinical, and clinical trial phases of new drug discovery and testing in humans.

A significant proportion of the time and expense of conducting clinical trials arises from the need to assure that the resulting data are accurate. Patients are selected, treated, and evaluated by a meticulous protocol, and results are recorded on standardized forms that are collected and analyzed by the sponsor or its designee. To ensure the validity and accuracy of the data, the pharmaceutical company periodically sends monitors to study sites to verify that patients are treated according to the study protocol and that the information is reported according to the study protocol. Monitoring alone can represent up to 30 percent of the costs of a clinical trial. Most pharmaceutical companies also have separate quality assurance departments to review forms and audit data and safety departments to monitor and prepare reports on adverse events.

From the pharmaceutical manufacturer's perspective, the key issue in data quality and integrity is how to collect only the information that is necessary to

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assess the safety and effectiveness of the experimental therapy, as well as how to ensure the quality and integrity of that information, while controlling costs and reducing the time consumed by the clinical trial process. From FDA's perspective, the key issue is ensuring that data submitted in support of an application are a valid representation of the clinical trial, especially as the data pertain to drug safety, pharmacokinetics, and efficacy.

BACKGROUND

Under the Federal Food, Drug, and Cosmetic Act, pharmaceutical manufacturers must obtain a research or marketing permit before beginning studies on certain commodities such as new human drugs, medical devices, veterinary drugs, and food additives and bringing them into interstate commerce. FDA approves these permits, and also regulates biomedical research whose results are to be submitted in support of an application for such a permit. FDA has two principal objectives in regulating this research: (1) to protect the rights and welfare of human research subjects and (2) to assure the quality and integrity of the biomedical research data used to support the initiation or expansion of clinical trials, the approval of new products and new indications, and the labeling of these products. The second objective is the subject of this report.

Organizationally, FDA works to protect human subjects and assure data quality and integrity through an intramural review process, conducted at its headquarters in Rockville, Maryland, and through the Bioresearch Monitoring Program, whose field agents inspect clinical research sites. Figure 1 depicts the review process for a New Drug Application (NDA), which is reviewed by the Center for Drug Evaluation and Research (CDER); the processes for medical devices and biologics are different in their details but follow the same general steps. The components of a marketing application are relatively uniform, and although the exact requirements are a function of the nature of the specific product or device, the application must provide all relevant data and information that a sponsor has collected during the research and development of the product.

In this system, the purpose of a clinical trial is to collect the information that will allow FDA to make regulatory decisions about the safety and efficacy of the product. The clinical trial protocol represents the agreement between the sponsor, investigator, and FDA as to how the clinical trial will be conducted. Consequently, an important focus of FDA reviews, both intramural and on-site, is data auditing to ensure that the study was conducted and analyzed as specified and that deviations from the protocol in conducting the trial or handling the data are adequately addressed. The purpose of such reviews is not only to rule out fraud, but also to ensure that the quality and integrity of the data are not compromised by sloppiness or poor compliance with the protocol. FDA does not have a set of standardized practices for its reviewers to follow in conducting these audits, but it is developing such good review practices.

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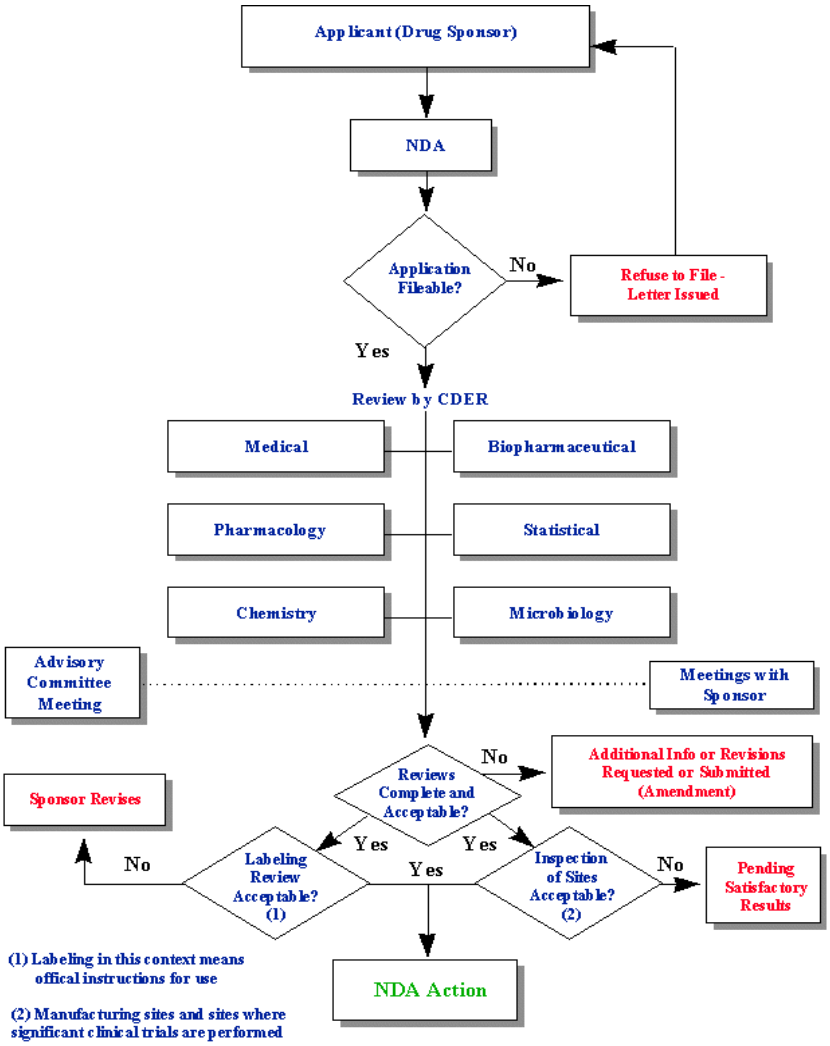

FIGURE 1. The Food and Drug Administration (FDA) works to protect human subjects and assure data quality and integrity through an intramural review process. The review process for a New Drug Application, which is reviewed by the Center for Drug Evaluation and Research, is depicted. The diagram does not accurately represent the review of a medical device and biologic application; however, it adequately depicts the steps related to such an action. SOURCE: FDA.

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OVERVIEW OF ISSUES

Presented by Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research,
Food and Drug Administration

The goal of improving health through the use of new medicines and medical devices cannot be achieved without public confidence in the clinical trials process. The purpose of clinical trials during drug development is to generate data on the safety and efficacy of a new product, data that will become part of the marketing application. The importance of informed consent and human subjects protection to the integrity of clinical trials has been widely discussed. Assuring the quality and therefore the usefulness of data from human clinical trials has received less attention, but it is also vital. Subjects should not be needlessly exposed to risks in trials that fail to yield valid data. In addition, it is essential that these data be reliable, because they form the basis for regulatory and medical decision making. For all these reasons, there is widespread agreement that such trial data should be of high quality.

Despite this fundamental agreement, many issues remain. The current processes for assuring data quality were developed individually in response to various problems or crises, rather than in a comprehensive quality management framework. Although the current system is successful, it is relatively expensive and time-intensive, may limit the overall investment in clinical trials, and may not provide the best-attainable quality for the degree of investment. Additionally, there is no consensus definition for "quality" as it applies to data from clinical trials. Finally, many changes that have the potential to affect data quality are occurring in the area of clinical practice and clinical trials. Widespread computerization of data entry and handling, use of CROs for performance of trials, the increased frequency of multinational trials, and the changes in the health care delivery system all may have impacts. The workshop described here explored these challenges.

The Workshop

Industry's role is to assure data quality and validity as the data are generated and processed. It does this by developing standard operating procedures and quality assurance checks at each stage of the trial, including the design of forms, investigator training, clinical site monitoring, and data cleanup. There is relatively little government guidance on the conduct of this phase of investigation. The International Conference on Harmonization recently developed a comprehensive governing document entitled *Good Clinical Practice*. This document has had a major impact on the conduct of clinical trials in Europe and Japan. In the United States, the Food and Drug Administration (FDA) has issued guidance on the monitoring of clinical trials and the maintenance of electronic records.

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The FDA role includes oversight of the Institutional Review Boards for the protection of human subjects, and the Investigational New Drug process for trials that are being performed in the United States. Once a marketing application is filed, FDA will inspect some of the clinical sites and compare the data in the application with those from among the sites. FDA also conducts data verification, a process that is highly varied because of the complexity and variety of the applications themselves. FDA is currently drafting "good review practices" internally.

In the past 10 to 20 years in the United States the quality of data from clinical trials has improved remarkably. Historically, most data problems have been the result of poorly trained investigators who either enrolled the wrong patients, did not follow the clinical trial protocol, did not record the required information, or had poorly designed protocols. Problems resulting from missing data or missing source records have also surfaced, as have problems resulting from faulty data entry, transposition, or analysis. Cases of outright fraud are rare. Fraud is a serious threat to public confidence, however, the prevention of fraud has been a major force in shaping the current system.

The current system for assuring data quality and validity during drug development and testing evolved over time, with parts of it enacted as problems emerged or in response to various crises. Consequently, the current system does not provide the harmonization and close integration of a prospectively designed system. During the workshop participants explored opportunities for improving quality by taking a systems approach.

Another issue explored at the workshop is the lack of a consensus standard for defining the quality of clinical trials data. Much of the industry quality control focuses on the detection of and elimination of missing data, transcription errors, or similar data problems. However, other aspects of trial conduct, such as how well investigators followed the protocol, are also extremely important to the validity of the trial results. Some of the discussions addressed how data quality in clinical trials should be assessed.

Several forces that will influence the future functioning of this system are at work. These include (1) new scientific discoveries, particularly in the area of pharmacogenetics; (2) the increasing automation of handling of clinical trials data, including remote data entry; (3) the potential role of managed care, which thus far has shown little interest in participating in clinical trials; and (4) the growth of outsourcing and the emergence of CROs. Each of these forces holds considerable promise for improving data quality but also has the potential to engender new problems for industry, government, private organizations, and consumers, and participants considered these during the workshop.

The members of the Roundtable identified three additional issues for speakers to address during the workshop. One issue was the question of how good is good enough. Although data quality is a continuum, there can be no "perfect" data set; instead, there may be a decreasing marginal benefit from pursuing such a goal. Quality data would therefore be defined as data that sufficiently support conclusions and interpretations equivalent to those derived from error-free data.

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A second issue concerned streamlining, which addressed whether the existing system is effective and efficient, and produces the highest-quality data for the lowest possible investment. If the answer was negative, the Roundtable members asked the speakers to identify how the system could be improved. Finally, Roundtable members asked the speakers what could be done to improve the quality of data generated from trials performed in some foreign countries.

The workshop was successful in broadening the dialog among FDA, industry, and the public on the subject of data quality and validity in clinical trials for the regulatory decision-making process. Although the participants presented and discussed many important issues such as the identification of opportunities for significant improvement in the overall process, the nature of any workshop is that it cannot serve as an exhaustive exploration of the subject matter being addressed. Therefore, the proceedings in this report contain only the information that emerged from the workshop itself.

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Presubmission and Submission

DATA COLLECTION

Presented by John R. Schultz, Ph.D.
Vice President and General Manager, Neuroclinical Trials Center
University of Virginia

A central issue in data collection is how to identify relevant, high-quality data that are readily available for appropriate decision making and to do so in a cost-effective manner. In this case, the phrase "high-quality data" refers to data that can be used without further revisions or data that will produce conclusions and interpretations that are equivalent to those that would be derived from error-free data, that is, data that are accurate, reliable, and fit for use. The key to producing such data is to engineer data quality into the entire clinical trial process.

Retrieval of High-Quality Data

The factors critical to the successful retrieval of high-quality data begin far upstream from the clinical trial and affect all stages of the clinical trial, as outlined in the following sections.

Scientifically Valid Protocol

The protocol should have clear, specific objectives in the form of a testable hypothesis. There should be a well-defined target population with specific criteria for inclusion and exclusion of study subjects. The study design should be relatively simple, because complexity frequently introduces error. The protocol should include all of the relevant endpoints with an identification of primary and secondary endpoints, and a detailed schedule of the activities and observations that will be included in the study. The protocol should also address those steps taken to assure data quality.

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Comprehensive Data Management and Analysis Plan

Elements of a data management and analysis plan include an annotated case report form with instructions on how to complete and code the form, a data entry manual, and a flowchart that describes the location and custodian of the data. A list of data variables, an analysis grid, and samples of the tables and graphics used for data presentation should also be available. Additionally, an explicit statement of data quality requirements should be developed to provide a standard for auditing purposes. The data management and analysis plan should also address the editing and auditing procedures that will be used, the methods used to calculate derived variables, and the methods used to validate software used in the study, as well as data security, system backups, and archival procedures.

User-Friendly Data Capture Instruments

Appearance is important for a form on paper and is even more important for a computer screen used for the electronic capture of data. The data capture instrument should allow data to be collected in parallel with the performance of the clinical routine, check-off boxes should be used if possible, and narratives should be avoided. Units of measure should be specified. Above all, the data capture instrument needs to be kept as simple as possible.

Good Clinical Testing Site Selection and Training Procedures

Overriding issues in good clinical testing site selection are access to target patient populations and determination of whether the site has the qualifications and expertise to meet the protocol requirements. Particularly important is the quality of the support personnel responsible for completing the case report form. One often overlooked question is determination of whether the site under consideration has concurrent studies, and how those studies may affect the quality and capacity of the site to conduct the proposed study. Training of personnel at the site begins with the investigator's brochure and continues with a review of a schedule of protocol activities and instructions for completing the case report form. Investigator and study coordinator meetings are recommended, particularly when they bring together personnel from different sites who are working on the same protocol.

Defined Site-Monitoring Procedures

Monitoring is required before, during, and after the study. At study initiation, monitoring involves protocol review, drug storage and accountability, and construction of the study file. After the first patient has been processed and the

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first set of case report forms has been completed, the data flow is reviewed to reduce the likelihood of errors. The results of the review are shared with collaborating sites.

Attention to Study-Specific Issues

The use of a means to code for adverse events and the use of concomitant medications is an important component of the study that requires careful planning and consideration. Laboratory procedures and data should be standardized, preferably through a central laboratory. Clinical supplies for the study should also be standardized.

Enhancing the Process

Three principal areas have the potential to enhance the quality and efficiency of this process.

Process Standardization

There is a great deal of literature to support the proposition that quality is achieved by the standardization of processes. In clinical trials for drugs, this means providing an integrated framework for study management, work flow, drug supply, and software development. It also means the need for an approach to handle medical events as well as an approach to data verification and validation.

Resource Review

More attention should be given to ensuring that the necessary resources are available to carry out the study. This includes identification of key personnel, additional human resources both at and away from the site, financial commitments outlined in a budget, and even clinical supplies and equipment. The entire activity must also have a time limit.

Enabling Technologies

Electronic mail and shared databases are very effective means of linking the personnel who monitor the trial at each site. Remote data capture has enormous potential, although there continue to be problems in the interface between the data capture and data management packages. Videotape instruction is effective and helps standardize procedures across sites. Videoconferencing can also rein-

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force the contact between personnel at the different study sites. Document sharing and interactive voice recognition are other enabling technologies.

Data Cleanup

A major cost element involves validation of the completeness, accuracy, and reliability of the data after the study, or data cleanup, particularly when there are open-ended sections of the data capture form for adverse events and concomitant medications. In addition, different variables might allow different quality standards. For example, primary variables that are closely related to the protocol objectives (e.g., patient identification and mortality rate) should have a much lower rate of error than secondary variables (e.g., leukocyte counts). In general, there is still a tendency to collect too many data.

MONITORING: INDUSTRY PERSPECTIVE

Presented by Eleanor Segal, M.D.
Senior Director, Drug Safety and Clinical Quality Assurance,
Chiron Corporation

Industry (e.g., pharmaceutical companies) monitors and audits clinical trial data for three reasons: first, to ensure the safety of the human subjects; second, to ensure that the company's investment results in a marketable product; and third, because it is required by regulatory agencies in the Code of Federal Regulations under 21 CFR 31.250:

> Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND [Investigational New Drug], maintaining an effective IND with respect to the investigations, and ensuring that FDA [Food and Drug Administration] and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

Although each company may structure its activities in different ways, responsibility for monitoring is typically borne by the following five principal groups:

1. The clinical research department includes medical monitors, often M.D.s, with a considerable amount of clinical experience. An even greater burden of monitoring, however, falls to the clinical research associates, who go out

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into the field to make sure that sites are properly initiated and that data are collected appropriately.

2. Most companies also have a separate clinical quality assurance department that conducts in-house file audits (to ensure that protocols are written correctly), and site and investigator audits (to match case report forms with patient charts), and that reviews informed-consent forms. Another function of the clinical quality assurance department is facilitation of audits when they are performed by regulatory agencies.

3. Members of the biostatistics and data management group, which is usually separate from the clinical research group, monitor all of the data received from the field and investigate emerging trends that might affect safety.

4. The drug safety department collects data on serious adverse effects. In many cases, clinical trial drug safety is handled separately from postmarketing drug safety.

5. The regulatory affairs group compiles expedited serious adverse effects reports and sends them to appropriate U.S. and international regulatory agencies within 15 calendar days after learning about the event.

Organizational structure, procedures, and data forms vary among pharmaceutical companies. For example, each company is responsible for assessing the relationship of a serious adverse event to the experimental drug; some companies record five to six subjective observations, whereas others simply use a "yes" or "no". These processes generate large amounts of data. A single draft serious adverse effects form may comprise five or more pages, and reconciliation of the data on this form with those on case report forms requires hours of effort by a study coordinator.

This process generates an enormous volume of data, and it is reasonable to ask whether all of these data are necessary and relevant. Frequently, the greater amount of data collected increases the risk of error and makes the task of reconciling data streams more difficult. Although many companies profess that they use data automation and electronic reconciliation techniques, the complexity of the data requires the use of trained personnel for the manual comparison of the data on separate printouts. To assure data quality and validity, regulatory decision making relies on the careful monitoring and review of data collection and data processing.

MONITORING: NATIONAL CANCER INSTITUTE PERSPECTIVE

Presented by Michaele C. Christian, M.D.
Associate Director, Cancer Therapy Evaluation Program,
Division of Cancer Treatment, National Cancer Institute

The National Cancer Institute's (NCI's) Cancer Therapy Evaluation Program sponsors up to 200 Investigational New Drug applications for investiga-

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tional agents and has up to 1,000 treatment trials, accruing over 20,000 new patients each year into studies at thousands of sites with thousands of investigators. In 1978, NCI filed quality control procedures with the Food and Drug Administration (FDA) that included guidelines for monitoring Phase 1 and 2 drug trials, a responsibility that is shared with a dozen multi-institutional Cooperative Clinical Trials Groups (CCTGs). These guidelines were revised and refined in 1982 and again in 1995. The goal of the program is to prevent data problems and to detect them when they occur. The components include training, study monitoring, data safety and monitoring committees, and on-site auditing. Audits serve as an educational tool because of the interactions between the auditors and clinical investigators.

Each participating institution is audited at least once every 3 years, although Phase 1 trials in which patients have increased risks are audited every 3 months. Institutions are notified 3 to 6 months before an audit. A list of the protocols and patient records to be audited is provided 2 to 4 weeks before the audit. The audit also includes at least three protocols and 10 percent of the patients who have accrued since the previous audit. The audit assesses Institutional Review Board approval, consent forms, and compliance and accuracy with regard to eligibility, treatment administration, response assessment, and toxicity reporting. The goals are to ensure the quality and accuracy of the data, compliance with federal regulations, and protection of the rights and welfare of human subjects. A preliminary report is issued within 24 hours of completion of the audit, and the final report is submitted within 70 days. NCI has established a computerized audit database to track the thousands of audits conducted by CCTGs.

Audits are rated "acceptable," meaning that no deficiencies or only a few minor deficiencies were detected; "acceptable needs follow-up," meaning that there were multiple minor deficiencies or a major deficiency that was not corrected before the audit; or "unacceptable." An assessment other than "acceptable" requires a written explanation and submission of a corrective plan to the CCTG and NCI. These rules and the standards for major and lesser deficiencies in each audit focus area were included in the 1995 guidelines.

From June 1995 through March 1998 there were 2,057 audits involving 675 protocols and 17,668 patient records. During that period, 6 percent of the institutions were rated "exceptional," 46 percent were rated "acceptable," 37 percent were rated "acceptable needs follow-up," and 11 percent were rated "unacceptable." Compared with the period from 1985 to 1994, the total number of deficiencies increased slightly, but most of the difference was in terms of lesser deficiencies. The increase in deficiencies may be due to greater and more consistent scrutiny, it may be the result of increased oversight by the Office for Protection from Research Risks, or it may reflect increased demands on Institutional Review Boards.

CCTGs are spending about $1.3 million, or 1.5 percent of their budgets, on audits. However, these expenditures do not reflect the full costs of auditing because the auditors are volunteers, and the sum does not include the costs for the sites to prepare for the audit. In addition, NCI sends auditors on CCTG audits

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and contracts with a clinical trials monitoring service to audit its cancer centers and selected grantees. NCI spends an additional $575,000 on CCTG audits, $193,000 on auditing Phase 1 clinical trials, and $104,000 on audits of Phase 2 and select Phase 3 clinical trials.

NCI is making a major investment in electronic data reporting and has already instituted World Wide Web-based reporting for Phase 2 clinical trials and adverse event reporting. The final system may take one of several forms, but a primary objective is to reduce errors by removing the need to reenter data that are already housed in another repository. One study across five clinical trials found that shifting from manual data entry to remote data entry with computerized edit checks can reduce error rates from 80,000 per million to only 200 per million. It can also cut the time to database closure from 22 weeks to 10 days.

Industry and NCI have different goals and procedures for data monitoring. Industry wants to get the drug to market in the shortest possible time, so it audits the individual trial and may not tolerate any errors with regard to efficacy or safety. NCI, on the other hand, wants to identify effective cancer therapies; it audits the institution in order to detect and prevent problems and to educate and train clinical investigators as a future resource for the conduct of clinical trials.

Although FDA regulations and guidance documents allow flexibility in the design of data management procedures, the requirements can become more rigid when they are standardized across a large institution or company. Industry, in particular, often has too much invested in a trial and is unwilling to take a chance on new or innovative approaches to data quality or site monitoring. In response, FDA is preparing final guidance for remote data entry. These efforts provide an opportunity for industry to work with FDA to develop guidance on other subjects such as defining a minimal data set that will meet regulatory requirements. These are important initiatives because the costs of collecting excess data and extensive monitoring are substantial and divert human and financial resources from other meritorious clinical trials.

DATA HANDLING AND CLEANUP

Presented by Kristin O'Connor, M.P.H.
Director, Data Management, Boehringer Ingleheim Pharmaceuticals

Greater communication and trust between industry and the Food and Drug Administration (FDA) are needed in terms of data handling and cleanup. Both go to great lengths and great expense to ensure data quality; the question is whether each is doing enough or too much, and whether the system could be simpler.

Industry's efforts toward ensuring data quality include the checking of source data in the field, the use of double data entry and computerized data checks, and review of data listings to identify outliers. These efforts also include means of validating systems and programs, as well as maintaining extensive

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documentation on data-handling plans, data inconsistencies, and agreement changes. FDA verifies these data using individuals with expertise in several areas: medical reviewers, statisticians, and auditors. In some cases, FDA statisticians reanalyze industry's data. Yet, it may be that some duplicative efforts by industry and FDA could be increasing the costs of clinical trials.

An alternative model for data management is demonstrated by the AIDS Clinical Trials Group, which cleans up data selectively by focusing on the fields important to the analysis. As another example of an alternative model, European regulatory agencies spend less time reanalyzing the data and more time evaluating the arguments set forth in the expert reports. The initiatives undertaken by the International Committee on Harmonization (ICH) are important steps toward standardization. However, the rate at which ICH guidelines are implemented varies among nations.

During an audit, FDA reviews all of the data and not just the primary endpoints of efficacy and safety. One perception among members of industry is that medical examiners do not like to find any errors or inconsistencies in the data, even in minor secondary variables, and that the application will lose credibility should minor errors occur. Industry's view is that there is no acceptable error rate. Consequently, industry spends additional money on further data cleanup, regardless of its effect on the key analyses.

FDA has been proactive in developing guidelines on archival submissions, electronic data formats, and other related topics. Obstacles to both the sponsor and FDA, however, include inconsistencies among FDA divisions in terms of hardware, software, computer literacy, and review standards. There is a need for greater communication and collaboration between industry and FDA to develop data management and data quality guidelines. An industry-FDA partnership could develop guidelines on the following:

- procedures for assessment of the robustness of key analyses and the effects of data inconsistencies;
- acceptable error rates for different fields in the database;
- minimal standard operating procedures for data management, as called for by ICH (e.g., how corrections are made and by whom, documentation of the process, and validation of programs that produce data tables and listings); and
- effective communication of quality assurance issues to FDA.

At present, a major cost factor may be an incomplete understanding by industry of FDA requirements for data quantity, quality, and cleanup. As long as technology continues to advance through faster computers and global databases without a corresponding improvement in the process, costs will continue to increase.

FDA may not have a clear enough understanding of the data handling and cleanup process. If a sponsor clearly documents focused data cleanup as well as error rates, the FDA should accept the sponsor's data unless FDA believes that safety, efficacy, or another important aspect may be adversely affected. Increased communication and collaboration involving medical, statistical, and regulatory

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specialists from both industry and FDA are important means to developing a common understanding of the requirements and processes that are acceptable to both. These efforts will prompt trust and achieve a common goal: production of a quality report with well-documented proof of safety and efficacy.

PREPARATION AND CONTENT OF MARKETING APPLICATIONS

Presented by Nicholas Pelliccione, Ph.D.
Senior Director, Worldwide Regulatory Affairs, Schering Plough

More active and rapid drug approval provides earlier benefits to the patient, the medical community, and the pharmaceutical industry. The decision on when to file a New Drug Application (NDA) must therefore strike a balance between the collection of enough data to support a complete and high-quality application and the time and expense involved in obtaining these data. Although some submissions consist of greater than 500 volumes of data, an NDA often requires less documentation.

The size of an NDA is primarily determined by the number of trials required to prove a drug's safety and efficacy. A study involving a drug for the treatment of cancer might require only a few hundred subjects, whereas one involving a drug used for the treatment of cardiovascular disease can require more than 10,000 subjects. Other sections of an NDA that require extensive documentation include sections on preclinical pharmacology and toxicology, carcinogenicity, chemistry, manufacturing and controls, and labeling information.

The scope of formal meetings between industry sponsors and the Food and Drug Administration (FDA) are defined in the NDA regulations. In addition, the sponsor's regulatory staff are frequently in verbal contact with FDA. The timing of the meetings before a request for an Investigational New Drug application, at the end of Phase 2, and before a request for an NDA helps advance a drug through the process; failure to take advantage of these meetings can lead to expensive delays.

A key consideration in filing an NDA is the number of pivotal trials necessary to demonstrate safety and efficacy in Phase 3 trials. In most cases, two adequate and well-controlled trials are needed to establish the safety and efficacy of a drug. For oncology or orphan drugs, however, the acceptability of one pivotal trial may be negotiated with FDA.

Another consideration involves the distinctions between superiority or equivalence trials. Superiority trials may require fewer subjects, since the difference in the effects of two drugs that investigators are trying to prove is much larger. Studies performed to demonstrate the equivalence of existing drugs require more subjects and thus more time. Consequently, discussions with FDA early in the NDA process will contribute significantly to proper experimental design, the use of adequate number of subjects in the trial, and a sufficient number of clinical trials.

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FDA and more recently the International Committee on Harmonization (ICH), have issued documents that provide guidance on the preparation of an NDA (Code of Federal Regulations, [21CFR 201, 312, 314, 600, 601]). These guidelines should be followed when clinical reports, statistical analyses, labeling, or other documentation is being prepared. Moreover, FDA recommends that companies build these guidelines into their development program. Adherence to ICH guidelines is equally important for companies desiring international approval of their drugs. More information on these guidelines may be found on the World Wide Web at the following URLs:

Center for Drug Evaluation and Research guidance source: http://www.fda.gov/cder/guidance/index.htm;

Center for Biologics Evaluation and Research guideline source: http://www.fda.gov/cber/; and

ICH guideline source: http://dg3.eudra.org.

FDA has improved its turnaround time on applications for new drugs, biologics, and devices. The Prescription Drug User Fee Act of 1992 (PDUFA) requires sponsors to pay a fee to have their applications reviewed. These fees were used to increase FDA staff requirements to meet the performance goals implemented by PDUFA. Both the fees and the performance goals were renewed in the FDA Modernization Act of 1997. As a result, a company can now depend on receiving an action letter in 12 months for a standard review and 6 months for a priority review. A key factor that ensures the effectiveness of PDUFA has been industry's understanding that NDAs must be submitted in accordance with established rules and that the application is complete upon filing or the NDA will not be reviewed. Since no sponsor wants its submission to be refused, the quality of submissions has increased significantly in the past 5 years.

PANEL DISCUSSION

During the first panel discussion, participants identified three key trends that may affect the response to issues addressed by workshop presenters. First, economic constraints on the health care system and safety concerns for patients suggest that there is a need for more information regarding tangible outcomes. Second, the pace of discovery is accelerating, and with it the number of trials that are under way is also increasing. Third, at least one effective therapy is available for most diseases, suggesting an increase in the number of equivalency trials, which require large numbers of subjects in whom differences in clinical outcomes are detected as a function of the particular therapy. These trends may lead to a collision between attention to minutiae, with its accompanying costs, and the information that society needs to choose safe treatments rationally. Four responses to this conflict are identified below:

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1. The intent of medical records is to provide a factual account of a subject's response and therapy. Auditing should critically review these records without biased assumptions on the data's accuracy.
2. There is a need for standards in data management, which would include standard nomenclature and differentiation between critical, high-quality data and secondary or background data.
3. More credentialed investigators and study coordinators are needed.
4. Sponsors may need to become more involved in paying patient care costs that are accrued specifically during approved clinical trials.

Participants discussed the development of a "decision science" that could establish quality control procedures on a scientific basis as one way to improve data quality and validity. For example, understanding of the current kinds of errors and the impacts of these errors on the interpretation of data and the conclusions drawn from these data needs to be improved. A means for the quantification of the level of acceptable data inaccuracy and the resulting sample size for clinical trials would enhance these efforts.

Improved technological capabilities have facilitated the rapid and voluminous data acquisitions by many investigators. A sharper focus on data quality and relevance rather than data quantity needs to be emphasized, especially with regard to the level of acceptable data quality. Quality data were then defined as data that support the same conclusions and interpretations as those derived from error-free data. Gathering of quality data requires greater transparency and sharing among study sponsors as well as with Food and Drug Administration (FDA), to achieve greater standardization and to increase confidence in innovative approaches. To accomplish this, there must be a greater level of communication between those who monitor the trials and the data analysts.

A perspective from the managed care industry was that the number of equivalency trials requiring relatively large patient populations is increasing. An opportunity provided by managed care is organized access to large numbers of potential enrollees in clinical trials. A concern expressed by the managed care industry was the possibility that long-term side effects of drugs would be undetected after an accelerated review process. These concerns involve both regulatory issues and industry's commitment to evaluating the long-term effects of these drugs.

The remaining discussion focused on the impacts of (1) multinational trials and (2) outsourcing of study coordination. Most panelists agreed that auditing of international data presents more of a challenge than auditing of data from studies conducted in the United States because of the use of different definitions for disease states and other variables. Studies conducted in developing countries (e.g., AIDS treatment trials) raise other sets of issues. Among these are ethical concerns. To reduce the cost of multinational clinical trials, some companies have set up European divisions, if only to decrease the expense of international travel. The use of International Committee on Harmonization (ICH) guidelines as the starting point for the standardization of operating procedures and labora-

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tory practices and cross-training of personnel from different quality assurance (QA) groups are approaches undertaken by most companies. These companies have learned that a high level of communication and cooperation is necessary to influence the ICH guidelines.

Contract research organizations (CROs) are not used by all sponsors. However, CROs are usually used for study coordination rather than for auditing or QA. Nonetheless, outsourcing does not completely replace internal resources, and high levels of communication and cooperation within a company are required. When data originate from CROs, most sponsors use the same computerized validation and other QA procedures that they would use if the data originated from internally performed studies.

Workshop participants discussed broader questions regarding the ultimate goals of data quality and the purpose of various QA procedures. For example, there was general agreement that the purpose of monitoring was to identify and correct data inconsistencies immediately upon their occurrence. Consequently, monitoring positively affects training and QA efforts. The National Cancer Institute model, as discussed earlier, addresses the issues of QA by focusing on the institution rather than on an individual study protocol. This is similar to the idea of having certified investigators conduct clinical trials.

Because each trial is unique, the panelists felt that it is inappropriate to take a uniform approach to data quality; perhaps, instead, each protocol should have an explicit data quality plan that addresses the need for monitoring and audits in terms of the characteristics and complexity of that particular study. Multicenter and multinational studies, for instance, typically require higher levels of monitoring. This reinforces the desirability of developing a "decision science" with methodologies or procedures that provide guidance on (1) protocol design, (2) acceptable error rates for different variables, and (3) the impact of data errors on the conclusions and decisions that result from a trial. This might provide industry an alternative way to achieve "data credibility" for its studies and for FDA applications.

Finally, there was general agreement that although monitoring improves data quality, too much data are collected in disparate formats and the increased cost of monitoring has not necessarily brought about a corresponding increase in data quality. Three options for further action were identified:

1. Simplify the process by designing the protocol correctly, selecting the right population for study, and identifying the right endpoints.
2. Decide which measurements of quality data should be used on the basis of evaluations of impact of data errors.
3. Simplify data collection and data monitoring by developing simpler and more consistent collection forms (e.g., for adverse events) and by standardizing approaches to monitoring.

The creation of a detailed evaluation of an intensively monitored and audited trial may be an initial step toward better understanding and communica-

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tion of the process. Such a report could identify the nature of errors and their impacts on the outcome of the study and could be used to make theories about the impacts of undetected errors. Although standardization and simplification are desirable goals, industry may be reluctant to be the test case for innovative approaches unless FDA approved such approaches by prior agreement.

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FDA Regulatory Review

PAPER AUDITING

Presented by Jay P. Siegel, M.D.
Director, Office of Therapeutics Research and Review,
Center for Biologics Evaluation and Research, Food and Drug Administration

The Food and Drug Administration (FDA) clinical reviewer audit focuses on whether a study report and related documents are an accurate reflection of the methods and outcomes of a clinical trial. Several factors determine the extent of an audit. One key factor is the importance of the data, that is, their impact on decision making and labeling. Those aspects of the conduct of the study which are deemed most critical to key conclusions (e.g., subject eligibility, level of drug compliance, and use of concomitant medications) will receive the most attention. During the audit, primary endpoints generally receive greater attention than secondary endpoints. The importance of the clinical trial to the overall Biologics License Application (BLA) or New Drug Application (NDA) is also considered; for example, is it a pivotal study or the principal source of safety data?

The extent of the FDA reviewers' audit of the data is also influenced by aspects of the study design, especially blinding, the objectivity of the endpoints, and whether the trial is designed to demonstrate equivalence or superiority. Lack of blinding increases concern about many aspects of study treatments and assessments. Equivalence studies are far more likely to have errors whereby an investigator will incorrectly accept the hypothesis that the drug has the desired effect (type I error). The general quality of the data report and the amount of missing data can also influence the intensity of the audit; it behooves the sponsor to include an open discussion of data deficiencies.

FDA's experience with a sponsor or investigator may also affect the nature and extent of the audit, particularly when there has been trouble with prior submissions or previous warning letters. FDA clinical reviewers have, to date, not usually considered the extent of monitoring and auditing conducted by the sponsor as a key factor in determining the extent and nature of their own audits. However, studying and attempting to validate the sponsor's quality assurance

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(QA) efforts can be powerful and effective. Of note, there is substantial variation in the approach to data quality auditing within FDA, and factors such as deadlines, workloads, and competing priorities can significantly affect the nature and extent of auditing.

FDA clinical reviewers use four basic auditing tools: (1) checks for compliance with the protocol, (2) checks for data consistency, (3) checks of clinical judgment calls, and (4) interactions with field inspectors. Compliance with the protocol is a central part of both medical and statistical reviews and focuses on inclusion and exclusion criteria, blinding, randomization, treatment, assessment, and analysis. Consistency checks include comparisons among centers in multicenter trials, comparisons of data over time, especially in studies with multiyear accrual of subjects, and checks of the consistency of data in various formats (e.g., tables, summaries, listings, and labeling). Assessments that require clinical judgment—such as cause of death, the cause of an adverse event, or success versus failure—are often critically evaluated by clinical reviewers. The clinical reviewer interacts with the field auditor to help decide which sites will be visited, which data will receive the closest scrutiny on-site, and which documents, if any, will be retrieved from study sites for further scrutiny.

Specific elements that are checked include randomization, blinding and unblinding, inclusion and exclusion criteria, treatment of more sensitive populations, the level of drug compliance, and the manner in which efficacy and safety data are reported. Other data points examined on a patient-by-patient basis include death, adverse events that lead to withdrawal from the study, and other serious adverse events. Specific approaches are used for audits of the various trial elements and data types.

Paper audits represent a substantial investment of FDA resources. Frequently, half or more of the time spent by clinical and statistical reviewers reviewing a marketing application is spent on assessing data validity in the broad sense.

CLINICAL SITE REVIEW AND INSTITUTIONAL REVIEW BOARD AUDITS

Presented by David Lepay, M.D., Ph.D.
Director, Division of Scientific Investigations
Center for Drug Evaluation and Research, Food and Drug Administration

On-site inspections complement paper audits in the Food and Drug Administration's (FDA's) efforts to ensure data quality and integrity in clinical trials. The Bioresearch Monitoring Program, which was established in the late 1970s, seeks to detect sloppiness or misconduct that might affect human subject protection, data integrity, and sound decision making on applications. It also seeks to prevent data quality and integrity problems before they occur. Inspections are conducted in accordance with published standard operating procedures that are updated every 3

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years and that focus on five groups: Institutional Review Boards (IRBs), clinical investigators, sponsors, contract research organizations, and monitors.

The primary purpose of an IRB review is to ensure the protection of the rights and welfare of human subjects. FDA's Bioresearch Monitoring Program conducts almost 200 IRB inspections per year, with routine inspections of historically compliant IRBs occurring once every 5 years, on average. However, the Bioresearch Monitoring Program focuses particular attention on new IRBs as well as those that oversee large numbers of studies or studies with large numbers of subjects, those that oversee higher-risk Phase 2 and 3 trials, and IRBs with a history of poor compliance.

Clinical investigator inspections concentrate on individual sites, validating data in the marketing application against original source data. This approach provides the opportunity to interact with clinical investigators and site managers and inquire firsthand about potential data integrity issues. Planning and evaluation of inspections requires communication and coordination not only with the study site, but also across FDA divisions, with sponsors, and with international regulatory authorities.

Review times have decreased since the passage of the Prescription Drug User Fee Act of 1992, but now FDA must meet even stricter time lines under PDUFA-2. This raises several issues:

- Will the Bioresearch Monitoring Program be able to appropriately expand the number of inspections, to address systemic problems that are discovered at one site and that are generalized across a multisite trial, and to have a positive impact on assessments of the study findings?
- Should the sponsor rather than FDA be responsible for performing validity assessments across the entire study when problems are disclosed at a single site?
- Is there sufficient flexibility in the PDUFA timeline to allow for contingencies?

The number of applications to FDA has increased, and with it the inspection workload has also increased. FDA's Center for Drug Evaluation and Research (CDER), for example, experienced a 40 percent increase in New Drug Application (NDA) filings between 1992 and 1997, from 73 in 1992 to 104 in 1997. The number of clinical investigator inspections has increased accordingly, to about 350 per year, but many applications involve scores of sites and investigators. As a result, it is not clear that FDA is inspecting enough sites or investigators per application to ensure public confidence in data quality and integrity. Table 1 presents the average time and costs required to conduct a clinical investigator or an IRB inspection.

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TABLE 1 Time and Costs of Each Clinical Investigator or IRB Inspection

Type of Inspection	Time (hours)*	Expense ($)
Domestic clinical investigator	70	7,350
Foreign clinical investigator	91	9,400
IRB	51	

*Includes preparation, conduct of inspection, and report write-up.

In deciding which sites to inspect, FDA tries to select those sites that have the greatest impact in terms of their contribution either to treatment effect or to the statistical significance of that effect (i.e., because the site contributes the greatest number of subjects). All reports of scientific misconduct received by FDA are investigated and may lead to inspections. Still, the selection of investigators for inspection is not by random sampling, and this precludes generalization of the inspection findings to the population of clinical investigators as a whole. Notwithstanding this caveat, results for the 302 domestic clinical investigator inspections conducted in 1997 indicated the following (Figure 2):

- 40.3 percent of domestic inspections exhibited no deviation from regulations and were classified as no action indicated (NAI);
- 56.3 percent of domestic inspections revealed objectionable conditions that were deemed correctable by action or reply by the investigator and were classified as voluntary action indicated (VAI);
- 3.3 percent of domestic inspections revealed major deviations from regulations or official action indicated (OAI).

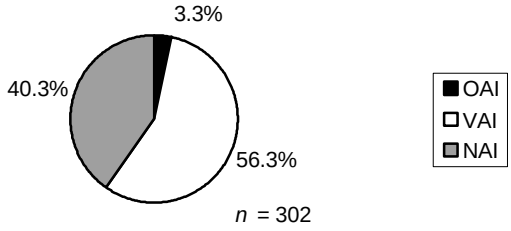

FIGURE 2. A total of 302 domestic clinical investigator inspections were conducted in 1997. A slight majority of inspections revealed at least minor deficiencies, and in most cases these deficiencies were of a nature that should be detectable, correctable, and preventable with effective monitoring.

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More than 50 percent of domestic clinical investigator inspections revealed at least minor deficiencies. In most cases, these deficiencies were of a nature that should have been detectable, correctable, and preventable with effective monitoring. The nature of these deficiencies has tended to remain constant over time: failure to follow the protocol (25 percent), problems with the consent form or process (21 percent), failure to maintain adequate source records (20 percent), failure to maintain accountability for investigational drugs (13 percent), and problems with adverse event reporting (5 percent).

Scientific misconduct is a rarity, accounting for no more than 1 to 3 percent of all inspections per year, but these cases receive a great deal of attention and can negatively affect public confidence in the clinical trial process. Moreover, seriously noncompliant investigators may work on multiple trials for multiple sponsors and may therefore affect numerous applications submitted to the agency. Failure analysis of six recent cases of serious scientific misconduct revealed that one clinical investigator was working on 91 Investigational New Drugs (INDs) or NDAs for 47 different sponsors (Table 2). At least 13 different sponsors had used two or more of these investigators, and 1 sponsor had used all six. Although most violations should have been detected by adequate monitoring, none were reported to FDA by the study sponsors. Disclosure of involvement with multiple trial or multiple sponsors may help identify and prevent noncompliance among investigators.

The number of clinical investigators is estimated to exceed 30,000 and is increasing at a rate of 8 to 10 percent per year. Clinical trial experience varies among clinical investigators. Other variables may also lead to a variable quality of work among clinical investigators, for example, differences in training, financial pressures, resistance to correction, inclination to delegate, and degree of personal involvement in the study. Qualifications, training, and experience also vary among monitors. This may be reflected in the degree of detail reviewed during inspection and the manner in which monitors respond to and report problems. The quality of monitoring may be a function of the monitoring visits themselves: their number, timing, and choice of sites. The degree to which monitors interact with investigators and sponsors is also important. Many monitors work closely with investigators, providing frank discussion of problems and recommendations for correction. When regulatory compliance cannot be achieved promptly, it is the sponsor's responsibility to terminate a seriously violative clinical investigator. Questions as to whether sponsors are meeting this particular responsibility have surfaced recently.

In addition to its domestic inspection program, CDER conducts international inspections when the data from international sites are pivotal to the regulatory decision-making process. The number of non-U.S. inspections increased from 5 in 1991 to 36 in 1997, reflecting the globalization of clinical trials. FDA has now conducted inspections of clinical investigators in 30 foreign countries. Serious data quality and integrity problems are more common in foreign inspections than in domestic inspections: in 1997, 17 percent of international inspections were classified by FDA as requiring additional regulatory actions, whereas

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only 4 percent of domestic sites received this classification (see Figure 2). Some small improvements have been noted among nations that participate in the International Conference on Harmonization (ICH). However, it remains an open question whether the broader adoption of ICH standards will lead to an improvement in data quality and integrity unless the adoption of such standards is accompanied by a mechanism for inspecting and enforcing these ICH standards. The latest revision of FDA's compliance program guidance manual, which includes reference to ICH good clinical practices and which provides guidance on computer systems, is in final review. The FDA's clinical investigator compliance program suggests that investigators keep copies of all source data and documents submitted to a sponsor to ensure FDA's ability to reconstruct the study while on-site.

TABLE 2 Failure Analysis of Recent Cases of Serious Scientific Misconduct

Clinical Investigator	No. of Applications	No. of Sponsors
A	91	47
B	49	25
C	43	21
D	21	17
E	12	6
F	6	6

FDA's review divisions and Bioresearch Monitoring Program are available to assist sponsors during the design and execution of clinical trials. This may include straightforward dialogue on the specific data to be collected and the importance of such data in supporting a safety or efficacy determination. In this context, CDER is also willing to meet with sponsors to develop a forthright understanding of the approaches and adequacy of trial monitoring and auditing proposals.

SANCTIONS

Presented by Stan W. Woollen
Deputy Director, Division of Scientific Investigations
Center for Drug Evaluation and Research, Food and Drug Administration

A major goal of Food and Drug Administration (FDA) sanctions is not to punish wrongdoers but, rather, to protect the integrity of the approval process and the rights and welfare of human subjects. Sanctions accomplish this by notifying affected parties that corrective action is required and excluding the data or the parties that have corrupted the process. Sanctions can be imposed against

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(1) clinical investigators, (2) sponsors, and (3) Institutional Review Boards. However, sanctions are rarely imposed because few people or organizations deliberately fail to comply with FDA requirements.

Sanctions available for use against clinical investigators include, in order of increasing severity, warning letters, consent agreements, formal disqualification, debarment, and prosecution under criminal statutes. *Warning letters* communicate the need for corrective action, and FDA follows up to see that corrective actions are taken. Warning letters are not sent to foreign investigators unless they are working under an Investigational New Drug application. Repeated or deliberate noncompliance or submission of false information leads to *formal disqualification*, barring the investigator from receiving investigational products. A formal disqualification requires a regulatory hearing and can be a time-consuming process that takes 2 to 4 years, during which time the investigator may continue to conduct studies.

An alternative is a *consent agreement*, which results in voluntary disqualification or negotiated restrictions on the investigators' activities, such as the number of studies an investigator may perform, oversight by another investigator, or third-party verification of data. Consent agreements reduce legal and administrative costs and give FDA the ability to tailor the sanctions imposed.

Debarment under the Generic Drug Debarment Act effectively prevents an individual from working in the drug industry. FDA will not accept or review applications from individuals or companies who have been debarred. Furthermore, *prosecution* under criminal statutes, for example, for fraud against the government, will also result in debarment, but these most extreme sanctions are rare.

Sanctions may be imposed against sponsors (and against contract research organizations that assume the responsibility of a sponsor) for problems in their FDA submissions and for problems that arise at study sites. Problems with submissions to FDA, such as false statements of material fact or patterns of error that result in widespread problems with data integrity, may be handled under the application integrity policy. Under its application integrity policy, FDA will defer substantive scientific review until a validity assessment is completed and may refuse to approve or may withdraw approval of an application.

Regulations related to monitoring at the clinical site and dealing with noncompliant clinical investigators are vague, and the appropriate sanctions are not defined. Frequently, sponsors fail to report the problems or the corrective actions that have been taken. For example, none of the sponsors who used six egregiously noncompliant investigators reported the investigators to FDA. In these cases, sponsors excluded the data but did not terminate activities at the site and were not required by regulation to report the investigators. Issues concerning how FDA can ensure proper monitoring of clinical sites and correction and reporting of problems in the face of existing regulatory requirements remain to be addressed.

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ASSESSMENT OF DRUGS

Presented by Murray Lumpkin, M.D.
Deputy Director for Review Management
Center for Drug Evaluation and Research, Food and Drug Administration

When the results of paper audit and on-site review are completed, two fundamental questions may determine their impact on decision making:

1. Are the problems with data integrity of such a magnitude that they raise questions regarding the integrity of the entire submission or the complete study?
2. If the problems are limited to a single site, will the integrity of the overall study be maintained if the data from the problem site are removed from the analysis?

Actual cases can illustrate the range of deficiencies that the Food and Drug Administration (FDA) encounters and how they influence the agency's assessment of New Drug Applications (NDAs) for molecular agents. In calendar year 1997, the Center for Drug Evaluation and Research (CDER) initiated actions on 235 NDAs, 121 of which were approved. Some 39 of the approved NDAs were for new molecular entities, and 37 of these were applications whose clinical data had been inspected. (The other two were orphan drug applications with nontraditional clinical data that were not amenable to conventional validation.) Those 37 approved NDAs involved inspections of 180 domestic sites, ranging from a low of 2 sites to a high of 13 sites per application. Of 180 sites, 65 were rated no action indicated and 112 were rated voluntary action indicated. Among the latter, problems at five of the sites were serious enough that FDA requested a formal response from the investigator. Only 3 of the 180 sites had a rating of official action indicated and are described below:

1. One investigator failed to follow the protocol for women of childbearing age, failed to notify the Institutional Review Board and sponsor of the death of subjects, enrolled 25 percent of his subjects from undocumented sites, and failed to retain source data at his principal site.
2. Another investigator failed to conduct required pregnancy tests, enrolled patients who were clearly ineligible, failed to collect the required samples, broke the blinding in the middle of the study, and had numerous discrepancies in the patient records, including treatment records that were dated before the individual's employment at the study site.
3. The third investigator failed to collect both baseline and study laboratory data, failed to report on prior or concomitant medications and adverse drug reactions, and had numerous discrepancies between source documents and case report forms.

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Of the five applications with a more serious rating of voluntary action indicated, the number and nature of the discrepancies were less egregious than those at sites with a rating of official action indicated, such as admission of a subject before collection of a signed consent, no record of institutional review board approval for protocol amendments, failure to randomize all subjects, and inability to produce original documents. These problems appeared to occur randomly and were deemed administrative rather than analytic. In such cases it is appropriate to ask if there is a reasonable explanation. If no explanation is forthcoming, however, the agency must determine whether there is a pattern of similar errors at other study sites and whether these errors affect the overall outcome.

In a recent case study, after an efficacy supplement for a cancer drug was approved, regulators discovered that 1 of 157 major sites involved in the trial had falsified clinical data. The original results were quite robust, and the results remained robust when data from the site with discrepant data were removed, but it raised questions about a drug on which many patients' lives depended. To restore public confidence in the overall study, it was necessary to show that this site with discrepant data was an isolated case. It was clearly impractical to audit all 157 sites in the United States and Canada. Alternatively, the agency developed a statistical model based on the impact of data from each site on the overall results of the study. Sensitivity analysis showed it would be necessary to eliminate data from all of the top 15 sites to reach a statistical value not significantly in favor of the drug.

On the basis of this model, FDA conducted full audits of 41 of the 157 sites. Ten were inspected for cause: three were previously inspected as part of the Bioresearch Monitoring Program review, two others (the site with discrepant data and the headquarters site) were inspected when the discrepancies emerged, and five other sites were inspected in response to questions that had been raised about data from the site. In addition, based on the statistical model that identified the top 15 sites, FDA inspected all of the top 4 sites, two-thirds of the next 11 sites, one-third of the remaining sites with more than 50 patients, and 15 percent of the 129 remaining sites that had fewer than 50 patients. The records of all subjects at each inspected site were reviewed.

In a large audit, examination of every data point in each source record and case report form is not practical. Accordingly, CDER selected 13 primary data points for examination of efficacy and developed standardized forms and instructions for field auditors. The resulting data were range checked and double entered into independent databases reconciled to identify missing and inconsistent data. Analysis showed that the overwhelming majority of source data were in agreement with the data in the NDA, and no pattern of discrepancy was discernible on either the treatment or placebo side of the study. A further stratified log-rank analysis revealed that even if all data from all sites that had any discrepancies were excluded, there would still be a significantly positive finding in favor of the drug.

This unprecedented audit, which occurred 10 years after the events transpired, was extremely resource-intensive and could not be applied to every ap-

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plication. These findings suggest that the majority of investigators are conducting clinical trials correctly. Most of the errors that do occur appear to be through carelessness or misconduct. An audit aims to seek a balance between the detection and prevention of errors without burdening conscientious investigators. The audit described above concluded that the methodologies developed for the design of clinical trials, including randomization, blinding, and monitoring, are the best defense against scientific fraud.

FDA has a long history of working with companies during the planning phase of their clinical trials. In the past 5 to 10 years more companies have been consulting with FDA because of the rising cost of drug development programs. Whether more intensive monitoring procedures produce a corresponding reduction in data problems remains to be determined.

ASSESSMENT OF DEVICES

Presented by Susan Alpert, M.D., Ph.D.
Director, Device Evaluation Office
Center for Devices and Radiological Health, Food and Drug Administration

About 12,000 manufacturers of medical devices have products on the market in the United States, and 65 percent of these manufacturers have fewer than 50 employees. Of the 5,000 products that go to market each year, 95 percent do so without any new data from clinical trials. When clinical trials are conducted, they are very different from those conducted for drug safety and efficacy. Clinical trials for medical devices are not always concurrently controlled and they are not always randomized, and masking or blinding of the prescriber is impractical or frequently not possible. The average clinical trial of a medical device involves 3 to 15 sites and about 200 patients, whereas hundreds of sites and tens of thousands of subjects are involved in drug trials.

Nevertheless, the Center for Devices and Radiological Health (CDRH) expects clinical trials of medical devices to be valid, well-designed, controlled evaluations of the safety and effectiveness of these new products. In 1992, CDRH enacted a more rigorous and organized monitoring program for the conduct of its clinical trials. Limited resources, however, restrict the number of site visits or extensive audits, even for smaller trials. The current goal is to monitor the sponsor site and up to three subsidiary sites for each premarket approval application (PMA).

In 1997, 28 of 46 sites with successful PMAs were audited. In some cases the company or the site had been visited recently and did not warrant an audit. In others the nature of the data did not warrant a traditional audit or there were too few subjects to make an audit meaningful. Of 28 audits, 3 (11 percent) required no action, 21 (75 percent) had minor discrepancies, and 4 (14 percent) had significant discrepancies:

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• In one case, informed-consent documents for some of the subjects at several sites were absent, and failure to follow the protocol was determined at another site. These discrepancies, however, did not have a significant negative impact on data quality.

• In a second case, the sponsor failed to monitor the trial, resulting in a number of inconsistencies in the data. These occurred primarily as a result of failure to report device failures, patient injuries, and other adverse events. CDRH required the sponsor to change the labeling and conduct a postmarketing safety study as a condition for approval.

• In a third case, one site failed to report adverse events, resulting in inadequate accountability for the experimental devices. These failures did not appear to be systemic, however, and a laborious reevaluation of the data from the remaining sites did not change the outcome of the PMA.

• In a fourth case, inadequate accountability, incomplete or inaccurate case report forms, and lack of Institutional Review Board approval at one site were observed. Because this was a critical product, CDRH worked with the investigators to reconstruct the entire study, an extremely intense audit that took more than a year. The reconstruction required the company to incur substantial financial costs to ensure that the product was indeed safe and would perform as expected.

The distribution and accountability of products, such as artificial hips or defibrillators, are critical areas to be monitored during clinical studies of medical devices. Often, far more devices than the number actually used—sometimes 100 or 200 percent more—are distributed to investigators because investigators will need a variety of sizes to fit the incoming population. When investigators fail to return the extra units, the PMA will lack information on the missing product and CDRH is unable to reconstruct the final disposition of a device.

In another case, the agency worked with a clinical practice group to conduct a retrospective study of pedicel screw implants, devices used to fuse and stabilize vertebrae in back surgery. There was no prior protocol, no case report form, and no consistent control for patients or treatment at the time that the study was undertaken. CDRH worked with investigators to construct retrospectively an entire data set. In addition, an independent monitor visited the major sites and conducted an audit of all sites. Problems with missing data and variations among physicians' decisions in terms of subject inclusion, monitoring, and measurements of outcome were widespread. The lessons learned from this audit demonstrated that having in place a protocol, a good case report form, and a good monitoring program has a positive impact on the quality of the data and the agency's ability to make a regulatory decision.

Sound regulatory decisions do not require perfect data. Instead, they require reliable data that accurately reflect the methods and procedures used and subject outcome. Critical errors are rare, fraud is more rare, and not every error has the same impact. It is the number of errors and where they occur that determine their impact on the analysis and the decision to exclude subjects or study sites or

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terminate the study. The case studies provided here demonstrate that audits increase the quality of the data across the board. In addition, audits strengthen the quality of investigators and clinical sites and improve data accuracy. Audits may also improve the ways in which companies conduct clinical trials and therefore help contain costs. Audits also provide the Food and Drug Administration the confidence needed to make an informed decision about marketing applications.

PANEL DISCUSSION

During the workshop's second panel discussion, one Food and Drug Administration (FDA) manager reported that, according to his informal survey, FDA statisticians have no established standard procedures or formal criteria for evaluating the quality of the data in the submissions that they receive. Instead, a neutral position is ensured as exploratory data analysis begins, with evaluation of the quality of the data occurring during the process. Both hypothetical questions and data are posed at this stage. In addition, an analysis and data verification are conducted with the sponsor's results. A disagreement in results is an indication of possible data error and poor data quality. In one case, for example, the protocol called for certain analyses, but the results of those analyses were not included in the submission. FDA personnel ran the analysis and obtained a significant result that would have been adverse to the product; they also found that summary statistics in one key table were not derived from the same analysis. The sponsor was unable to adequately state the reasons for these inconsistencies in data quality.

When FDA statisticians find unexpected gaps or errors in the data, an "untitled letter" rather than a warning letter is issued. Although clinical investigators and sponsors are not required to respond, they often do, explaining that regulatory requirements were not understood completely and expressing gratitude for having the opportunity to correct and learn from the mistakes that they made. These types of situations reveal the need for additional training of investigators by sponsors, given the fact that FDA personnel are spending a considerable amount of time finding errors and discrepancies that should have been revealed during the monitoring process. Many problems and questions are also being identified during Institutional Review Board (IRB) audits, thereby increasing the pressures on IRBs. Thus, this may be an area that is ripe for collective, cooperative action by sponsors and FDA.

Workshop participants identified the need for collaborative systematic improvement in the area of data quality as more prudent than trying to find data inconsistencies after the fact when auditing is conducted. This is an important consideration because both the number of independent sites for clinical research and the number of clinical investigators will continue to grow. Most of the physicians trained by U.S. medical schools, however, are not specifically trained in clinical investigation, which may contribute to a low level of prestige for clinical investigators within the academic environment. This raises questions about the

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need to modify medical education and to certify clinical investigators, as is already done for other subspecialties. Although certification of clinical investigators may also be desirable for research coordinators, there is a need to explore alternative incentives (and reimbursement patterns) that reward quality rather than volume.

These ideas, which were well received by the panel members, further support the findings that 50 percent of physicians who participate in clinical trials are first-time investigators, which confirms that there is still much naivete among the investigators at the clinical sites. The Association of Clinical Research Professionals, which represents 7,600 members, recently spent $500,000 on programs to certify 800 clinical research associates and 3,500 clinical research coordinators in 37 cities. There is now an interest in the development of a similar program for certification of clinical investigators and institution of a code of ethics. These topics were addressed at an April 1998 meeting of the Drug Information Association which was conducted after this workshop (see the box on the Drug Information Association).

Drug Information Association

The Drug Information Association (DIA), founded in 1964, is a nonprofit, multidisciplinary, member-driven scientific association with more than 20,000 members. Its membership consists primarily of individuals from regulatory agencies; academia; contract support organizations; pharmaceutical, biological and device industries; and from other health care organizations. DIA provides a neutral global forum for the exchange and dissemination of information on the discovery, development, evaluation, and utilization of medical products and related health care technologies. The meetings, workshops, and training courses sponsored by DIA are responsive to the rapidly evolving, multidisciplinary needs of its international membership.

Participants expressed concern about the possible absence of an informed consumer's perspective in discussions on clinical trials and research. For example, if a goal of clinical research is to provide patients with access to continually improved quality of care, then progress toward risk-free therapy needs to be based on the best possible information and needs to include opinions from informed consumer groups. Moreover, patient participation was recognized as paramount to clinical research, and this requires an informed and willing consumer population. Lack of informed patient participation could undermine public confidence and trust in the regulatory process.

The National Breast Cancer Coalition (NBCC) was noted as one example of a consumer group that has played a vital role in outreach for participation in and accrual in clinical trials. NBCC trains community activists and works with com-

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panies in designing programs that permit expanded access to clinical trials (see the box on The National Breast Cancer Coalition). Two important issues for this group include (1) a lack of coordination between FDA and industry and (2) the failure of FDA to join with the National Cancer Institute (NCI) and other agencies and organizations to lobby insurance agencies for reimbursement for the costs associated with patient participation in FDA and NCI clinical trials.

Ensuing discussions requested that panelists focus on the related issues of hierarchical data sets and two-tiered monitoring. They were asked to consider whether both sponsors and FDA are spending proportionately (1) too much effort on traditional audits and inspections, which focus on record keeping, or (2) not enough effort on proactive questions such as definition of error, sensitivity analyses, tolerance of error, and how to design a simpler and more efficient data system. One panelist characterized the traditional audits and inspections as "mindless monitoring" as opposed to "looking at process." Another panelist cited the extreme example of investigators who create a separate set of source documents for clinical trials that are totally divorced from the patient's main medical records because they believe that FDA requires them. Although this practice was rejected as a waste of time and a source of new inconsistencies, it does reinforce the need for FDA to communicate its expectations more clearly. Efforts to build quality into clinical trials are generally not part of the pretrial discussions between FDA and sponsors.

Most panel members agreed that there is a need to define data standards and to distinguish between primary and secondary data. Several suggested that International Committee on Harmonization guidelines (which describe a quality assurance program without specifically requiring it) were a first step in that direction. Others suggested that safety data would always be important, but that a commitment to postmarketing surveillance is also needed, especially if premarketing testing is streamlined. However, a panelist expressed concern that once the patient leaves the clinical trial setting, it becomes almost impossible to distinguish between the therapeutic effect of a drug or a device and the natural course of a disease. The long-term effects of Fen-Phen on cardiac valves, for example, were not detected through systematic surveillance but were identified by astute observations by medical specialists. Managed care organizations could make a considerable contribution to systemic long-term surveillance because of the wealth of data on drug use and patient health over time that they harbor. However, thus far they have expressed little interest in making such a contribution.

Several participants suggested that the best way to simplify databases was not to collect too many data in the first place. Such a protocol may require prior agreement to determine which data should be collected and which data should be excluded. Should this become a viable alternative, the secondary questions on the case report form need to be disregarded so that data are not collected. There is a pressing need for sponsors and FDA to work together to decide which data are not as important and to agree on the areas on which monitoring and auditing should focus. Several panelists also suggested that the investigators' meeting with FDA should be conducted earlier and that the Institutional Review Board

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be invited to address data sets and data quality measures as early as possible in the process.

Other panelists expressed reservations about having FDA work closely with sponsors in planning the design of a trial. They expressed concern whether it would be prudent for a sponsor to conduct an objective assessment of the outcome of a clinical trial after working with an FDA reviewer in defining data sets or monitoring schemes. Although some panelists indicated that an objective assessment was a management issue that needed to be handled by FDA, others rejected the idea. The latter group argued that by clarifying expectations beforehand, FDA would in no way compromise scientific integrity. FDA reviewers explained that by helping sponsors correctly conduct the study, it would not mean that the results would be favorable or that the product would be approved. The alternative—knowingly allowing inadequate trials to go forward—would simply be irresponsible in terms of both getting drugs approved and protecting patients.

National Breast Cancer Coalition

The mission of the National Breast Cancer Coalition (NBCC) is to help eradicate breast cancer through action and advocacy. From its inception, this nonprofit, grassroots organization has acted as an advocate not just within the government, but also within industry and the scientific community. The coalition is a powerful voice that speaks on behalf of breast cancer patients, activists, and others concerned with the breast cancer epidemic.

NBCC has been successful in bringing together breast cancer activists from across the country. The sponsored conferences by the coalition are designed to educate and train breast cancer advocates; they have provided beginner and advanced advocacy training as well as information on breast cancer research and public policy. Through its network of activists—consisting of more than 450 organizations and 58,000 individuals—NBCC has initiated fundamental changes over a 7-year period. Some of its accomplishments during this period have included the following:

- increased federal appropriations for breast cancer research more than sixfold;
- created a grassroots network across the country;
- heightened awareness through three nationwide signature campaigns;
- brought awareness of the issue of breast cancer to the presidential level;
- initiated the development of an unprecedented multi-million-dollar breast cancer research project within the U.S. Department of Defense;
- precipitated and participated in the development of the National Action Plan on Breast Cancer—a collaboration of government, science, private industry, and consumers;

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National Breast Cancer Coalition *Continued*

- developed a science course designed to educate advocates in the basic science, medical language, and concepts of breast cancer, as well as in the breast cancer research decision-making structure;
- developed a program to educate members of Congress and their staffs on the science, health care, and medical practices that are important for implementation of policies related to breast cancer;
- launched a breast cancer political campaign;
- brought together more than 250 breast cancer activists from 43 countries to help create or expand networks and collaboration, as well as to share information, ideas, and strategies in the fight against the disease;
- developed a program to educate and train the media in the tools essential for critical analysis of information on breast cancer before relaying that information to the public; and
- initiated the Clinical Trials Project, which educates NBCC members on the importance of clinical trials and trains them to work in partnership with industry and the scientific community to expedite the conduct of clinical trials. Such trials provide an opportunity to involve consumers in the search for answers to research questions that may subsequently result in important new advances in the field.

Among the many reasons why NBCC has been successful in achieving its mission and has realized many accomplishments since its inception has been its persistent focus on three goals:

- research—increasing appropriations for peer-reviewed research and working within the scientific community to concentrate research efforts on breast cancer prevention and finding a cure;
- access—increasing access for all women to high-quality treatment and care and to clinical trials to treat breast cancer; and
- influence—increasing the influence of women who live with breast cancer as well as other breast cancer activists in the decision-making process.

An industry representative found it encouraging that FDA reviewers were discussing the probability of collecting fewer data and asked when it would be most appropriate to hold such discussions in the review process. FDA personnel suggested that such discussion should be integrated into meetings on protocol design, before the clinical trial is actually launched. Although a regulatory agency may never have a concrete answer to what is considered sufficient data or sufficient quality, it is best for sponsors to discuss such questions early in the development process.

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Summary of Issues

Janet Woodcock, M.D.

The workshop was successful in broadening the dialogue between the Food and Drug Administration (FDA) and industry on the subject of data quality. This dialogue clarified many expectations on both sides, notably by dispelling the myth that FDA cannot accept errors in a submission. Major points stressed repeatedly throughout the workshop included recognition by FDA (1) that there will be errors in the clinical trial process, (2) that the existence of errors does not mean that there is fraud, and (3) that a reasonable number of minor errors is acceptable, as long as they do not compromise the reliability of the overall data set or the inferences that are being drawn from the data about the safety and effectiveness of the product. FDA reviewers described several instances in which they approved products despite sloppiness and even fraud at isolated sites, largely in part because the agency went to extraordinary lengths to reconstruct data sets and restore confidence in the reliability of the inferences drawn from those data.

FDA deals with errors in almost every submission that it reviews. Foreign trials seem to have particularly high error rates. Although outright fraud is extremely rare, the violating investigators are likely to be conducting different trials for other sponsors. Although FDA feels that many of the errors they find would have been detected by adequate monitoring, several speakers questioned whether the entire system—industry in its monitoring and FDA in its reviews—is devoting too much attention to minor details when it should instead be looking for a better way to assess data quality or even a way to build data quality into the system.

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Directions for the Future

A major finding of the workshop was the need for collaborative systematic improvements. Related themes included the need for greater openness and communication; broader involvement of stakeholders, including consumer groups; greater efforts to build quality into the process; and careful attention to maintaining public confidence and the scientific integrity of the clinical trials and regulatory process. In the course of the workshop, participants identified a number of topics about which further discussion might contribute to this effort. The Roundtable members therefore proposed that a 1-day symposium be convened to focus on the following three topics identified as important follow-up activities to the workshop: (1) clinical investigator training, (2) the role of consumers, and (3) better integration of the Food and Drug Administration (FDA) and industry with regard to monitoring.

FDA is making plans to convene a working group of its members as well as with the Institute of Medicine (IOM), National Institutes of Health, and stakeholders in clinical investigations (credentialing bodies, university representatives, clinical trials societies, pharmaceutical industries, and study personnel representatives) to discuss clinical investigator training issues. Topics expected to be covered in this first follow-up activity include training of clinical investigators for pediatric trials, clinical pharmacology, informed-consent issues, and the most effective type of training.

This workshop report highlighted the fact that the goal of improving health through the use of new medicines cannot be achieved without public confidence in the clinical trials process. Subsequently, this objective cannot be achieved without participation of the public and without bringing into the spotlight the importance of informed consumer groups' opinions. An effective means of measuring the public's confidence in the process by which new investigational drugs are evaluated is their willingness to participate in clinical trials. Although

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to date plans for addressing the third proposed topic are still in their infancy, IOM has initiated communication with FDA and industry to begin making preparations to convene a symposium on consumer involvement issues, the second follow-up activity identified by the Roundtable members. A major goal of this symposium will be to demystify the drug development and drug safety process for consumers. Messages on such issues to consumers have been developed by FDA as well as by Public Citizen and the Consumer Federation of America, consumer organizations that watch over the activities of federal agencies. Some of the proposed discussion topics may include messages to consumers on drug development and drug safety in the areas described below.

DEVELOPMENT

- ways to determine whether a drug is safe and effective,
- whether new drugs need to be more effective and safer than older drugs,
- knowledge of long-term safety of new drugs at time of approval,
- quick review of new drugs by FDA for serious and life-threatening diseases, and
- which patients can have access to experimental drugs that have not completed the final FDA review.

SAFETY

- determination of whether the benefits of a drug outweigh the risks,
- acknowledgment of the fact that risks exist in taking every drug,
- difficulty in determining all of the individual adverse reactions to a prescription drug,
- voluntary nature of the adverse drug reaction reporting system and the fact that health professionals are therefore not required by law or regulations to report any adverse drug reactions to FDA,
- the fact that manufacturers are required to report to FDA adverse drug reactions reported on any of their medicinal products, contrary to the requirements for health professionals,
- monitoring of adverse drug reactions by FDA to determine whether labeling changes are necessary or whether the drug should be removed from the market,
- encouragement of consumer reporting of an adverse reaction to a medication to one's health care provider or directly to FDA, and
- insistence that consumers obtain a drug's approved product labeling from the pharmacist before taking a new drug.

By demistifying the drug safety and development process, it is hoped that public confidence and public participation in the clinical trials process will be maximized.

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Final Comments

In 1997, 49 new therapeutic compounds for 39 diseases affecting an estimated 160 million people were introduced onto the market. Drug development is a lengthy and uncertain process, taking up to 15 years, with less than 1 in 10,000 compounds making it from preclinical testing to marketing. This process is also expensive, costing at least $300 million and possibly more than $500 million for each drug that successfully makes it to market. An individual clinical trial can cost as much as $100 million. Because at least 15 percent of clinical trial expenses are related to monitoring activities, however, more prudent and efficient monitoring has the potential to substantially reduce the costs of clinical trials.

An important way to improve monitoring is to reduce the amount of data collected. An average 12-month clinical trial with 2,000 patients will generate up to 3 million data points. A potential 10 million opportunities for error are estimated per trial, given that the data are handled at least six times, for example, in the clinic, during double data entry, and during cleanup activities. Even with a "good" error rate of 1 in 1,000, this would yield 10,000 errors. However, actual error rates are often much higher. Therefore, sponsors should be collecting only those data that are directly related to the outcome variable. Collection of superfluous data generates an enormous number of errors and may compromise a sponsor's and the Food and Drug Administration's (FDA's) ability to interpret the results accurately.

The challenge at hand is to collect the correct data and to monitor the data collection process more effectively and efficiently. Key elements in this effort include the following:

- Engineer data quality into the process by creating systems that limit the opportunity for errors.

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• Standardize formats and procedures, where possible, to increase efficiency.

• Simplify the experimental design because complex studies have the potential to yield more errors.

• Plan ahead by defining the proper data set needed and specifying requirements for data quality (e.g., error rates of 1 to 5 per 1,000 for primary endpoints, but 2 or even 5 errors per 100 for secondary endpoints).

• Clarify expectations by discussing with regulators the types and amount of data collected, the extent of monitoring, and the methods for data analysis.

A major theme that emerged from the workshop was that of partnerships. It was proposed that industry sponsors work with FDA before a clinical trial to define a coherent set of data that will demonstrate safety and efficacy and to set up an appropriate monitoring plan to ensure the quality of those data. Although FDA has been open to such efforts and considerable progress has been made in several areas, there is room for continued improvement. Other points emerged during the workshop and are described below.

ACTION

During the past 20 years the relationship between FDA and the pharmaceutical industry has evolved from an adversarial one to a more collaborative interaction. This strengthened relationship now provides an opportunity for FDA and industry to move forward on the issues of hierarchy in data quality assessment, early planning to build quality into the process, and improved communication.

EDUCATION AND TRAINING

Education of the public on the FDA review process and on the technical obstacles that industry must face when it develops even a single drug and brings it to market is important for enlisting consumer confidence. However, an even greater need is education of investigators, Institutional Review Boards, industry sponsors, and even regulators. They need to be educated that the goal is not merely passage of an inspection, but rather the generation of quality data that will support the inferences drawn from a study. There may also be a need for more specific training (and possibly credentialing) of clinical investigators, as well as clinical research associates and clinical research coordinators.

COMMUNICATION

The pharmaceutical industry spends substantial amounts of money on monitoring activities not required by FDA. Consequently, industry needs to be

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more forthcoming with FDA about its concerns and expectations. Conversely, FDA needs to reach internal consensus about its needs and expectations and then communicate that consensus externally. Similarly, FDA, sponsors, and investigators must communicate earlier and far more candidly about their expectations with regard to (1) the kinds of data that are most important to the outcome of the study, (2) adequate or acceptable ways to generate those data, and (3) the standards against which those data will be evaluated. There is also a need for more assessment and candid communication on how reimbursement issues affect data quality.

DEFINITIONS

Definition of permissible error rates and the level or degree of data quality was a central theme throughout the workshop. Unfortunately, little information in the public domain defines data quality. Moreover, definitions of error rates and quality data may vary among the training, monitoring, and auditing phases of an investigation. Consensus on definitions needs to be developed for each phase of the clinical trial.

FUNCTIONAL QUALITY

The goal of data quality is not efficiency, but is reliability to provide adequate information to support the inferences made in the application. Perhaps the application should include a new section describing the steps taken in a clinical trial to achieve a high level of data quality. The audit function may be an iterative mechanism for the identification of better processes and better outcomes.

INTERNATIONAL DATA

International clinical trials are becoming increasingly important sources of data for drug development and marketing. More attention needs to be devoted to the monitoring and review of internationally derived data, as well as therapeutic efficacy differences.

Other Areas for Consideration

The workshop provided an overview of the collection, validation, monitoring, and FDA review of the clinical trial data necessary for the development of a new drug product. It was successful in assessing the current situation and identifying potential solutions to many of the problems outlined in the workshop discussions. For instance, it was established that the situation would improve greatly and costs would diminish if the amount of data collected were dimin-

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ished and if the data to be analyzed were prioritized in a hierarchy of importance and relevance over the long term. Additionally, the workshop outlined some of the challenges with regard to the quality and validity of data from clinical trials that lie ahead. These points, some of which are addressed below, will warrant further consideration.

It became evident during the discussions not only that it is important to plan for clinical trials, but also that it is critical that data quality be addressed in terms of postmarketing surveillance for drug safety and effectiveness for the development of drugs in general. Such surveillance is becoming increasingly important because it monitors drug use under non-ideal, real-life conditions and is significant in making Phase 3 clinical trials more meaningful in terms of determining the number and length of trials. Multiple instances of drug recall or modifications of drug labeling on the basis of observations made during postmarketing drug surveillance in the United States warrant the need for this type of activity to prevent adverse drug reactions.*

The quality of the clinical investigators was thoroughly discussed at the workshop, at which participants pointed out that many are inexperienced and not formally trained to perform clinical trials. A related challenge concerns the quality of the FDA reviewers of clinical data. There is considerable variability in experience, training, and expertise among FDA reviewers. Although FDA reviewers are generally skilled in determining how best to design a protocol, this may not always be the case due to the complexity of the process. FDA biostatisticians, who may not always be open to newer methods of data analysis, may also encounter difficulties in providing the best protocol. These are important issues that may warrant further investigation.

Another issue that bears consideration as an outgrowth of the workshop concerns the accrual of patients in clinical trials, which is a significant issue in the rate of development of a new medication. Accrual may not be an issue in terms of the quality of clinical data. However, if investigators are certified to conduct clinical trials, it is essential that there be a sufficient number in each medical discipline throughout various geographic locations to provide an adequate number of patients in a reasonable period of time. A challenging situation results when physicians are not willing to transfer eligible patients to a clinical investigator for participation in a trial because of lost income. A solution could include the conduct of clinical trials in managed care facilities.

As alluded to in some of the workshop discussions, the issue of site initiation visits is an important consideration in terms of data quality. Many site initiation visits are made by contract research organizations, and in general such organizations may be better equipped at instructing the clinical coordinators than

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*For more information, refer to Lazarou J, B Pomeranz, and P Corey. Incidence of adverse drug reactions in hospitalized patients. *JAMA* 279(15):1200–1205, 1998, and Wood A, CM Stein, and R Woosley. Making medicines safer—the need for an independent drug safety board. *The New England Journal of Medicine* 339(25):1851–1854, 1998.

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are the clinical investigators. The quality of data may therefore improve if medical monitors perform the site initiation visits.

Another issue that emerged from the discussions concerned blinded studies. Although the extent of an FDA reviewer's data audit is influenced by numerous factors, such as blinding of study designs, objectivity of the endpoints, and whether the trial is designed to demonstrate equivalence or superiority, lack of blinding increases concern about many aspects of the treatment and assessment of the patients in a study. This implies that an in-house safety evaluation is not possible with blinded studies. One remedial action could be establishment of an external safety monitoring committee in the protocol.

Error rates were heavily discussed at the workshop. FDA, for instance, is fully aware that errors will likely occur in the clinical trial process. FDA is also aware that the occurrence of errors does not indicate that fraud has played a part in the trial. A reasonable number of minor errors is acceptable, as long as the errors do not compromise the reliability of the overall data set or the inferences that are being drawn from the data about the safety and effectiveness of the product. Although an error rate of 1 in 1,000 is considered good, actual error rates are often much higher. Because the collection of excessive data generates a large number of errors, compromising a sponsor's and FDA's ability to interpret the results accurately, it was suggested that only data directly related to the outcome variable be collected. A related issue that is worthy of consideration is the fact that the greatest errors generally occur when a notation describing a patient's incident is incorporated into the medical record. Additionally, the medical record frequently includes contradictory information because it represents the subjective account of an individual provider in an unstructured format.

Participants indicated that sponsors frequently fail to report problems or take corrective action with respect to monitoring of clinical sites and noncompliant clinical investigators, largely in part because regulations are vague and the appropriate sanctions are not defined. In many cases, it has been found that sponsors exclude the data but do not terminate trial activities at the site. A point to be considered in such cases is the fact that exclusion of data creates problems. With patients entered into the randomization scheme, removal of patients after randomization jeopardizes the basis for statistical inference. Additionally, exclusion of patients after randomization could jeopardize the operant's inference, which would be comparable to the inclusion of imperfect data.

The revised compliance guidance manual used by FDA suggests that investigators maintain copies of all source data and documents. Given the nature of medical practices in the United States, it is not uncommon for practices to be bought, sold, or go out of business within a matter of months. An issue worthy of consideration is identification of who owns the data and documents when medical practices go through these changes. It is necessary to propose some type of plan to deal effectively with such occurrences.

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APPENDIX A

Workshop Agenda

INSTITUTE OF MEDICINE
NATIONAL ACADEMY OF SCIENCES

ROUNDTABLE ON RESEARCH AND DEVELOPMENT OF DRUGS, BIOLOGICS, AND MEDICAL DEVICES

Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision-Making

April 14–15, 1998

National Academy of Sciences Auditorium
2101 Constitution Avenue, N.W., Washington, D.C.

TUESDAY, APRIL 14: DAY ONE

OPENING PLENARY

8:30 a.m. **Welcome**
Kenneth Shine, M.D.
President, Institute of Medicine

Opening Statement, Charge to Participants
Ronald Estabrook, Ph.D., *Roundtable Chair*
Virginia Lazenby O'Hara Professor of Biochemistry
University of Texas Southwestern Medical Center

8:45 a.m. **Overview of Issues**
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration

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SESSION I: PRESUBMISSION

9:00 a.m. **Data Collection**
John R. Schultz, Ph.D.
Vice President and General Manager, Neuroclinical Trials Center
Virginia Neurological Institute, University of Virginia

9:30 a.m. **Questions and Answers**

9:45 a.m. **Monitoring**
Eleanor Segal, M.D.
Senior Director for Drug Safety and Clinical Quality Assurance
Chiron Corporation

10:15 a.m. Michaele Christian, M.D.
Associate Director, Cancer Therapy Evaluation Program
National Cancer Institute, National Institutes of Health

10:45 a.m. **Questions and Answers**

11:00 a.m. **BREAK**

11:15 a.m. **Data Handling and Clean-up**
Kristin O'Connor, M.P.H.
Director, Data Management
Boehringer Ingleheim Pharmaceuticals, Inc.

11:45 a.m. **Questions and Answers**

12:00 p.m. **LUNCH**

SESSION II: FDA SUBMISSION

1:30 p.m. **Preparation and Content of Marketing Applications**
Nicholas Pelliccione, Ph.D.
Senior Director, Worldwide Regulatory Affairs
Schering Plough

2:00 p.m. **Questions and Answers**

2:15 p.m. **Panel Discussion I: Presubmission and Submission**
Moderator: Susan Alpert, M.D., Ph.D.
Center for Devices and Radiological Health
Food and Drug Administration

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Panelists:
Robert Califf, M.D.
Duke Clinical Research Institute

Michaele Christian, M.D.
National Cancer Institute, National Institutes of Health

Susan Ellenberg, Ph.D.
Center for Biologic Evaluation and Research
Food and Drug Administration

Frank Hurley, Ph.D.
Quintiles Transnational Corporation

Kiyoshi Kuromiya
Critical Path AIDS Project

David Lepay, M.D., Ph.D.
Center for Drugs Evaluation and Research
Food and Drug Administration

Mike McGarvey, M.D.
Blue Cross/Blue Shield of New Jersey

Kristin O'Connor, M.P.H.
Boehringer Ingleheim Pharmaceuticals, Inc.

Nicholas Pelliccione, Ph.D.
Schering Plough

John R. Schultz, M.D.
University of Virginia

Eleanor Segal, M.D.
Chiron Corporation

3:45 p.m. **BREAK**

4:00 p.m. **Plenary Review of the Day, Discussion of Issues, and Plans for Tomorrow**
Michael Clayman, M.D.
Vice President, Cardiovascular Research and Clinical Investigations, Lilly Research Laboratories, Eli Lilly and Company

5:00 p.m. **ADJOURN, RECEPTION**

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WEDNESDAY, APRIL 15: DAY TWO

SESSION III: FDA REGULATORY REVIEW

8:30 a.m. **FDA Review: Paper Auditing**
Jay P. Siegel, M.D.
Director, Office of Therapeutics Research and Review
Center for Biologic Evaluation and Research
Food and Drug Administration

9:00 a.m **FDA Clinical Site Review and IRB Audit**
David Lepay, M.D., Ph.D.
Director, Division of Scientific Investigations
Center for Drug Evaluation and Research
Food and Drug Administration

9:30 a.m. **Questions and Answers**

9:45 a.m. **BREAK**

10:00 a.m. **Sanctions**
Stan Woollen
Deputy Director, Division of Scientific Investigations
Center for Drug Evaluation and Research
Food and Drug Administration

10:15 a.m. **Assessment**
Murray Lumpkin, M.D.
Deputy Director for Review Management
Center for Drug Evaluation and Research
Food and Drug Administration

10:45 a.m. Susan Alpert, M.D., Ph.D.
Director, Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

11:15 a.m. **Questions and Answers**

11:30 a.m. **LUNCH**

1:00 p.m. **Panel Discussion II: FDA Review**
Moderator: Whaijen Soo, M.D. Ph.D.
Vice President, Clinical Sciences
Hoffmann-La Roche, Inc.

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Panelists:
Susan Alpert, M.D., Ph.D.
Center for Devices and Radiological Health
Food and Drug Administration

William Fairweather, Ph.D.
Office of Epidemiology and Biostatistics
Food and Drug Administration

Charma Konnor
Center for Devices and Radiological Health
Food and Drug Administration

Robert Levy, M.D.
Wyeth-Ayerst Research

Murray Lumpkin, M.D.
Center for Drugs Evaluation and Research
Food and Drug Administration

Roger Meyer, Ph.D.
American Association of Medical Colleges

Jay Siegel, M.D.
Center for Biologics Evaluation and Research
Food and Drug Administration

Frances Visco, J.D.
National Breast Cancer Coalition

William Waggoner, Ph.D.
Essex Institution Review Board

Stan Woollen
Center for Drugs Evaluation and Research
Food and Drug Administration

2:30 p.m. **Wrap-up Discussion**
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
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Ronald Estabrook, Ph.D.
Roundtable Chair

Virginia Lazenby O'Hara
Professor of Biochemistry
University of Texas Southwestern Medical Center

3:30 p.m. **ADJOURN**

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APPENDIX B

Speakers and Panelists

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APPENDIX C

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APPENDIX D

Glossary and Acronyms

This Glossary is intended to define terms and acronyms that are commonly used throughout this report as well as those terms and acronyms that are commonly used during the Food and Drug Administration (FDA) regulatory review process. This glossary is not all-inclusive. New terms and new uses of existing terms will emerge with time and advances in technology. Definitions for the terms and acronyms herein were compiled from a multitude of sources, which are listed at the end of the Glossary.

Adverse drug reaction: Any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This World Health Organization definition excludes therapeutic failures, intentional and accidental poisoning (i.e., overdose), and drug abuse. Additionally, this also does not include adverse events due to errors in administration or noncompliance (taking a drug at more or less than the prescribed dosage).

Analysis: Comparison of the outcomes for the study and control groups.

Audits, Food and Drug Administration: Process by which the Food and Drug Administration reviews the clinical data as part of clinical drug trials.

Benchmark standard: A criterion of evaluation or measurement used as a reference point in observation.

Bioresearch Monitoring Program: A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of Food and Drug Administration-regulated research. This program monitors sponsors, Institutional Review Boards, clinical investigators, and nonclinical laboratories involved in the testing of investigational devices.

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Blinding: A study design feature that helps ensure that bias does not distort the conduct of a study or the integration of its results. In a single-blind study, only the clinical investigators are aware of which intervention (e.g., investigational drug or control) each patient is receiving. In a double-blind study, neither the patients nor the clinical investigators know the identity of the intervention. In a triple-blind study, neither the patients, the clinical investigators, nor the committee monitoring the response variables is told the identity of the groups.

Carcinogenicity: Producing or tending to produce cancer.

Case report form: A standardized data entry form used in a clinical trial. Generally, all information collected in trials appears on Case Report Forms (CRFs), or is referred to and explained by CRFs.

Center for Biologics Evaluation and Research (CBER): A center of the Food and Drug Administration whose mission is to protect and enhance the public health through regulation of biological and related products including blood, vaccines, and biological therapeutics according to statutory authorities (www.fda.gov/cber).

Center for Devices and Radiological Health (CDRH): The center of the Food and Drug Administration whose responsibility is to ensure that medical devices are safe and effective, including ensuring the minimization of exposure from radiation-emitting electronic products (www.fda.gov/cdrh).

Center for Drug Evaluation and Research (CDER): A center of the Food and Drug Administration whose mission is to ensure that safe and effective drugs are available to the American people (www.fda.gov/cder).

Clinical reviewer: A person with responsibility for critically evaluating a medical perspective information contained in a marketing application.

Clinical studies: The class of all scientific approaches used to evaluate medical means of disease prevention, medical diagnostic techniques, and medical treatments. Investigational and marketed prescription drug evaluations plus over-the-counter drugs are included.

Clinical trials: Medical research studies conducted with volunteers. Each study is designed to answer scientific questions and to find better ways to prevent, detect, or treat human medical conditions.

Clinical trial protocol: Document describing a clinical study and how it is to be conducted. A protocol includes the objectives of the study, the study design, a description of the drug and the dosage, the experimental procedure, handling of adverse reactions, how the results will be analyzed, and patient consent and clearance provisions.

Comparative studies: Studies conducted to determine statistically whether one procedure is better than another.

Compliance: A quantitative indicator of whether a set of procedures or practices were carried out in accordance with established guidelines or standards stated in the protocol of a study.

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Concomitant medication: An additional therapy or regimen that is either self-administered or prescribed concurrently with a study therapy.

Contract Research Organizations (CROs): Organizations that are hired by companies to perform specific studies on a given topic.

Cooperative Clinical Trials Group (CCTG): A community-based organization that conducts research involving human volunteers under agreement with the National Institutes of Health.

Data: All collected and recorded information on patients considered for enrollment or actually enrolled in a trial.

Database: A collection of data files that are organized in a specified manner and that are accessed by designated personnel for designated purposes.

Defibrillator: An electronic apparatus used to counteract atrial or ventricular fibrillation by the application of brief electroshock to the heart, either directly or through electrodes placed on the chest wall.

Discovery: The early phases of the overall drug development process dealing with the synthesis of or search for compounds and the screening process developed to identify lead compounds.

Disease: The condition in which the functioning of the body or a part of the body is interfered with or damaged. In a person with an infectious disease, the infectious agent that has entered the body causes it to function abnormally in some way(s). The type of abnormal functioning that occurs is the disease. Usually, the body will show signs and symptoms of the problems that it is having with functioning. Disease should not be confused with infection.

Double blinding: In a clinical trial, a procedure for issuing and administering treatment assignments by code number to keep study patients and all members of the clinical staff, especially those responsible for patient treatment and data collection, from knowing the assigned treatments so that the information does not influence some measurement, observation, or process.

Drug (from the Food and Drug Administration Food, Drug, & Cosmetic Act): (1) a substance recognized by an official pharmacopoeia or formulary; (2) a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; (3) a substance other than food intended to affect the structure or function of the body; (4) a substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

Drug development process: The entirety of the activities and decision making that must be completed from the identification of a lead compound to regulatory agency approval for marketing of a compound as a new drug product.

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Effectiveness: The desired measure of a drug's influence on a disease condition. Effectiveness must be proven by substantial evidence consisting of adequate and well-controlled investigations, including human studies by qualified experts, which prove that the drug will have the effect claimed in its labeling.

Efficacy: A relative concept referring to the ability of a drug to elicit a beneficial clinical effect. This may be measured or evaluated by using objective or subjective parameters and in terms ranging from global impressions to highly precise measurements.

Equivalence trials: A trial typically conducted to demonstrate that there is no clinically significant difference between a standard and an experimental treatment. The study is designed with the desired outcome being equivalence in efficacy, while immediate toxicity, long-term adverse effects, or costs may be demonstrated to be advantageous for the experimental treatment.

Federal Food, Drug, and Cosmetic Acts of 1938 and 1962: Law that requires a manufacturer to prove the safety and effectiveness of a drug before it can be marketed.

Food and Drug Administration (FDA): A public health agency charged with protecting American consumers by enforcing the Federal Food, Drug, and Cosmetic Act and several related health laws (www.fda.gov).

Food and Drug Administration Modernization Act of 1997 (FDAMA): Major legislation focused on reforming the regulation of food, medical products, and cosmetics. Some of the provisions of the act include prescription drug user fees, Food and Drug Administration initiatives and programs, information on off-label use and drug economics, risk-based regulation of medical devices, and standards for medical products.

Form FDA 483: An official Food and Drug Administration form on which any objectionable conditions and/or practices noted during an inspection are listed. A Food and Drug Administration investigator issues Form FDA 483 to an establishment (e.g. investigator, sponsor, monitor, contract research organization, or Institutional Review Board) at the conclusion of an inspection.

Gene therapy: The process of introducing new genes into the DNA of a person's cells to correct a genetic disease or flaw.

Generic Drug Enforcement Act of 1992: A law authorizing the Secretary of Health and Human Services to impose debarments and to take other action to ensure the integrity of abbreviated drug applications under the Federal Food, Drug, and Cosmetic Act.

Genomics: The study of genomes, which includes genome mapping, gene sequencing, and gene function.

Good Clinical Practices (GCP): Food and Drug Administration-promulgated guidelines governing the conduct of clinical studies from which data will be

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used to support applications for marketing permits (New Drug Applications).

Good Clinical Practices (GCP) document: An international ethical and scientific quality standard for the design, conduct, recording, and reporting of trials that involve the participation of human subjects.

Good Review Practices: A Food and Drug Administraation initiative designed to promote standardization of the quality and consistency of reviews of New Drug Applications and Investigational New Drugs.

Institutional Review Board (IRB): Any board, committee, or other group of experts and laypeople formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to ensure the protection of the rights and welfare of the human subjects.

International Conference on Harmonization (ICH): An organization with representation from the regulatory parties of the European Union, Japan, and the United States, established to create common standards for safety, efficacy, and quality of medical products (www.ich.org).

Investigational agents: A medical product (e.g., drug, biologic, or medical device) used for research purposes to diagnose, prevent, or treat disease.

Investigational New Drug (IND): Status given an experimental drug after the Food and Drug Administration approves an application for it to be tested with humans.

Investigational New Drug (IND) application: Application that a drug sponsor must submit to the Food and Drug Administration before beginning tests of a new drug on humans. The Investigational New Drug application contains the plan for the study and is supposed to give a complete picture of the drug, including structural formula, animal test results, and manufacturing information.

Managed care: Arrangements for integrated health care delivery and financing that are designed to provide appropriate, effective, and efficient health care through organized relationships with providers. Includes formal programs for ongoing quality assurance and utilization review, financial incentives for covered members to use the plan's providers, and financial incentives for providers to contain costs. Managed care plans vary greatly in the degree to which benefit coverage is offered, monitored, and conditioned upon certain criteria being met by the subscriber and the subscriber's primary care physician.

Medical device: A diagnostic or therapeutic contrivance that does not interact chemically with a person's body.

Monitor: A person who oversees the ongoing evaluation of a continuing process to determine when and if changes in that process are necessary for reasons of efficiency, data quality, safety, and so forth.

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National Cancer Institute (NCI): The federal government's principal agency for cancer research and training. The National Cancer Institute is a component of the National Institutes of Health (www.nci.nih.gov).

National Institutes of Health (NIH): A group of institutes and related support structures responsible for funding basic and applied research in the health field. The National Institutes of Health also initiates and carries out medical research on an intramural and extramural basis (www.nih.gov).

New Drug Application (NDA): An application requesting Food and Drug Administration approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for Food and Drug Administration review, including chemistry, pharmacology, medicine, biopharmaceutics, and statistics, as well as for anti-infectives and microbiology.

Oncology: The study of diseases that cause cancer.

Orphan drugs: Drugs (and other products) for the treatment of a rare disease that affects fewer than 200,000 people or a drug that may offer little or no profit to the manufacturer but that may benefit people with rare diseases.

Outliers: In statistics, an observation so distant from the central mass of data that it is considered an obvious mistake or anomaly that should be removed from the data whether or not a cause of the deviation can be found.

Outsourcing: Hiring of contract employees to perform support services rather than use of a company's own employees.

Patient: In the clinical trial setting, patient refers to any subject involved in the trial.

Pharmaceutical: A medicinal drug.

Pharmacokinetics: The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, metabolism, and excretion.

Pharmacology: The science that deals with the origin, nature, chemistry, and effects of drugs and the uses of drugs for living organisms.

Phase 1 trials: The first trials in humans that test a compound for safety, tolerance, and pharmacokinetics. The Phase 1 trials usually use healthy volunteers. For known toxic compounds, such as anticancer agents, only patients with the targeted illness are used.

Phase 2 trials: The pilot studies that define efficacy and further test safety with selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Dose and dosing regimens are assessed for magnitude and duration of effect during this phase.

Phase 3 trials: Expanded clinical trials intended to gather additional evidence of effectiveness for specific indications and to better understand safety and drug-related adverse effects. Phase 3 trials are usually large multicenter trials that achieve substantial safety experience and may also include specialized studies needed for labeling.

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Pivotal trial: A clinical trial for a marketing application that is considered an essential component to supporting the safe and effective use of a medical product.

Placebo: A pharmacologically inactive agent given to a patient as a substitute for an active agent. When trials with placebos are conducted, the patient is not informed whether he or she is receiving the active or the inactive agent (the placebo).

Postmarketing surveillance: Requirement that drug firms report to the Food and Drug Administration the adverse experiences from the use of all marketed drugs of which they are aware. If the adverse experiences result in death, prolonged hospitalization, or permanent disability, the firm must report the incident within 15 days of its notification of the adverse experience. All other adverse experiences can be reported on an annual basis.

Premarket Approval Application (PMA): An application requesting Food and Drug Administration approval to market a new medical device for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for Food and Drug Administration review.

Prescription Drug User Fee Act of 1992 (PDUFA): Requires manufacturers to pay fees for certain new drug applications and supplements, an annual establishment fee, and annual product fees.

Quality assurance (QA): Any procedure, method, or philosophy for collecting, processing, or analyzing data that is aimed at maintaining or improving the reliability or validity of the data and the associated procedures used to generate them.

Remote data capture: A process by which information is entered directly into a computer or a centralized database without being recorded on paper.

Safety: A relative concept referring to the freedom from harm or damage resulting from adverse reactions or physical, psychological, or behavioral abnormalities that occur as a result of drug or nondrug use. No drug is completely safe or without the potential for side effects. Before a drug may be approved for marketing, the law requires the submission of results of tests adequate to show that the drug is safe under the conditions of use in the proposed labeling. "Safety" is thus determined on a case-by-case basis and reflects the drug's risk-versus-benefit relationship.

Site monitoring: The act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, Good Clinical Practices, and the applicable regulatory requirements.

Special populations: A subset of the population that may be more sensitive than the general public to the effects of a medical product (e.g., pediatric and

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geriatric populations and patients with compromised liver or kidney function).

Standard operating procedure (SOP): Established or prescribed methods to be followed routinely for the performance of designated operations or in designated situations.

Superiority trial: A trial typically conducted to demonstrate that there is a clinically significant difference between a standard and an experimental treatment. The study is designed with the desired outcome being superiority in efficacy in favor of the experimental treatment.

Therapeutic agent: A drug, biologic, or medical device used for research purposes in the treatment of disease.

Toxicology: The scientific study of poisons, their actions, their detection, and the treatment of the conditions produced by them.

Trial: Any tentative or experimental action conducted to obtain data used to make some judgment or conclusion.

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