FDA: The Mission and the Message

David H. Woodbury

Medical Imaging Section, Division of Medical Imaging, Surgical and Dental Drug Products, Food and Drug Administration

This is the third article in a six-part series on new radiopharmaceuticals. Upon completion of this article, the nuclear medicine technologist will be able to (1) discuss the history of the FDA, (2) describe the process for new drug approval, (3) list possible causes for delay in new drug approval and the initiatives currently in place to streamline the review process, and (4) understand how the nuclear medicine community can improve its review submissions.

J Nucl Med Technol 1993; 21:8–10

The stated mission of the Food and Drug Administration (FDA) is "to assure efficacy and safety in marketed medicinal agents and medicinal devices." The process by which this mission is achieved is authorized by Congress; formalized by codes, regulations, and guidelines; and interpreted and implemented by scientists, lawyers, biostatisticians, engineers, and a number of project managers of varied backgrounds.

The FDA currently employs approximately 7,000 people who work in one of the Agency's 30 Washington, D.C. offices or in one of the 160 field offices located throughout the United States. The Division of Medical Imaging, Surgical and Dental Drug Products, is responsible for review of and recommendations for new radiopharmaceuticals. It has 2 administrative physicians, 6 reviewing medical officers, 1 radiopharmacist, 2 chemists, 2 pharmacologists, 1 microbiologist, and 2 project managers (former nuclear medicine technologists) who are responsible for the review of new drug agents submitted for use in medical imaging.

During the past decade, increasing criticism has been directed toward the Agency by industry, academia, and nuclear medicine practitioners, due to the length of time necessary to review, process, and approve new radiopharmaceuticals. Conferences have been held with the FDA commissioner, discussions have been held with the current secretary of the Department of Health and Human Services (HHS), letters have been written to the director of the Center for Drug Evaluation and Research, and several meetings have been held with Division staff for explanations as to the length of time needed for approval of new radiopharmaceuticals (2–10 yr with a mean of 39 mo). These drugs are generally considered to be safe and effective by those in the nuclear medicine community, for use in the diagnosis of disease.

In an agency as large and complex as the FDA, the solution to the problems are not simple, and the causes for delay are substantive. Some delays are inherent in the review process and some are the responsibility of the sponsors and investigators submitting investigational new drug (IND) applications and new drug applications (NDAs). In order to help those in the nuclear medicine community understand the approval process and the changes currently underway within the Agency, I will address the following topics: the historical perspective of drug regulation; the current process for new drug approval; causes for delay in NDA approval; current FDA initiatives to streamline the review process; and suggestions on procedural changes that the nuclear medicine community can make to improve their NDA submissions.

HISTORY OF DRUG APPROVAL

Until 1906 there was no regulation of drugs used in humans. There were no restrictions on sales or advertisement claims and no obligation to prove the safety or efficacy of drugs or devices. Unproven claims were rampant and product purity was suspect. In this milieu, Congress approved the Federal Pure Food and Drug Act (*1*) that gave the FDA authority to remove drugs from the market place, but only if the FDA could prove that the drug was not pure or that it was unsafe.

The Pure Food and Drug Act was amended in 1938 following an epidemic of deaths traced to the use of diethylene glycol as a solvent in the untested preparation of a new class of medicinals—sulfonamides. The amended Act required applicants to provide the FDA with evidence of drug safety prior to marketing, to provide toxicity studies, and to develop product labeling that summarized dosage, indications of use, chemical class and structure, and known probability of untoward reactions (*2*).

For reprints contact: David H. Woodbury, MD, Parklawn Blvd., HFD 160, Rockville, MD 10857.

The primary emphasis on safety was maintained until early in the 1960s when the increasing incidence of phocomelia, a rare birth disorder, was traced to the mildly hypnotic drug Thalidomide, which was used during early pregnancy. Reaction to the teratogenicity of the drug occurred worldwide, and this encouraged the U.S. Congress to promulgate the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug, and Cosmetic Act (*3*). These amendments require extensive pharmacological and toxicological research be submitted to the Agency before human testing; the description of three progressive phases of clinical studies before submission of an NDA; the demonstration of substantial evidence of effectiveness through adequate and well controlled studies; inclusion of records and report requirements by applicants; and strengthening of prescription drug advertising requirements. An important difference is that now during the clinical phases of a study, *efficacy* of the product must be documented in a substantial manner. Indeed, all drugs marketed between 1938 and 1962 had to be proved effective retroactively.

NDA APPROVAL PROCESS

The above background provides a basis for understanding the NDA approval process and time projections for completion. There are four phases of investigation, each having specific requirements.

Nonclinical Phase. Studies must be performed in at least two species of animals to portray absorption, distribution, metabolism, and excretion of the new drug in the animals and to establish potential dose levels and estimate dosimetry. Toxicity, mutagenicity and pyrogenicity studies are performed; pharmacodynamic studies are performed to determine organ/body response to the new agent as a function of dose and time. These studies are designed to demonstrate that the new agent is safe for human trials.

Phase I. Initial clinical studies are usually performed on normal volunteers. These studies attempt to depict pharmacodynamic and pharmacokinetic parameters of the new agent in humans. Toxicology studies may be continued or completed. Safety in humans is the major determinant in this phase of the study.

Phase II. Controlled studies are initiated in 50 to 200 patients known or suspected of having the clinical malady for which the new agent is being developed. Dose-range studies and alteration of protocol may take place during this phase as an attempt is made to demonstrate differences in response or effects from those proposed in the original hypothesis.

Phase III. Placebo controlled, comparator controlled, or open trials are initiated in large numbers of patients (up to 1000 or more), in multiple centers, to assess the ability to replicate data in at least two separate independent investigations and to verify and tabulate adverse reactions to the test agent. In trials of diagnostic radiopharmaceuticals, the number of patients required for approval may be smaller, since the usual safety parameters are easily proven and adverse reactions are rare. In this phase efficacy is paramount, although safety is of ongoing concern. To date, the low incidence of untoward reaction in trials utilizing radiopharmaceuticals has been reassuring.

Upon completion of Phase III studies, the sponsor collates all data, both nonclinical and clinical, from drug synthesis to Phase III trials, and submits an NDA to the FDA for review, evaluation, and final approval prior to marketing. The NDA is reviewed by an investigator in each discipline (pharmacology, microbiology, chemistry, biostatistics, and medicine) to ensure that the new product is safe and effective for widespread human use. An investigator from the compliance division visits the manufacturing plant to inspect and ensure that all phases of manufacturing are controlled and reproducible. Medical institutions and manufacturing facilities are also inspected by the division of scientific investigation to vadidate clinical and chemical data. Following written input from all reviewing disciplines and consultants (if needed), the NDA is rated as approved for marketing, approvable providing certain conditions are met, or nonapprovable by the Division. An approved recommendation is sent to the Center for Drug Evaluation for review. The Center sends a letter to the commercial sponsor either granting approval or stating disapproval of the NDA.

CAUSES OF NDA APPROVAL DELAYS

There are many reasons for delays along the approval path. Some of the more notable causes are discussed below.

Sponsor-generated delays. Delays may occur if the format or substance of submitted data is poor. Some IND/NDA submissions include over 140 volumes of clinical data. If organization of the material, indexing, or pagination is not cohesive, the review process is extended.

FDA-generated delays. There is a mandated 30-day response time for IND submissions and a 180-day response time for NDA submissions. If a reviewer receives two or three INDs while reviewing an NDA, it is difficult to meet the requisite response time for each NDA submission. INDs have priority.

Any one of the reviewing disciplines can place a "hold" on a submission until deficiencies in the submission are addressed by the sponsor and cleared by the FDA. The deficiencies may be clinical, chemical, or pharmacologic, and the time required to effect the changes may be weeks or years depending on the severity of the deficiency.

Until a few years ago, many review reports were handwritten, then given to secretaries for transcribing. Weeks of delay could ensue as the author and secretary corrected typographic errors.

In some instances, deficiencies have been brought to the attention of sponsors, but between the time of notifying the sponsors and receiving a reply to the deficiencies there is a change in corporate or FDA personnel and a breakdown in follow-up as the new personnel familiarize themselves with the process.

Delays can also take place in the approval process as the documents progress from one level of authority to the next for consideration and approval.

FDA INITIATIVES TO STREAMLINE REVIEW PROCESS

The causes of delay in the review process are multifactorial and responsibility for the delay is shared by the FDA and sponsors. Responding to the need to decrease time for processing new radiopharmaceuticals, the Division of Medical Imaging, Surgical and Dental Drug Products has instituted several initiatives over the past few months that, when fully implemented, should impact favorably on the review process. These initiatives are summarized below.

1. FDA representatives will meet with sponsors at every stage of the submissions (i.e., prephase I, II, and III and preNDA) to enhance communication, so that the sponsors have a better understanding of the FDA's legal requirements for protocol design, patient distribution, statistical parameters, and quality assurance. This should decrease the number and type of discrepancies that cause delays.
2. A system has been implemented to track each submission from the time it reaches the Division document room until final approval or disapproval. The hope is to identify those areas in the review process that consistently cause delays and to develop a system to improve processing in these areas.
3. The group leader, medical reviewing officers, and radiopharmacist, meet biweekly to discuss problems common to the group that might be addressed and corrected expeditiously.
4. All reviewers have been provided with personal computers and word processing software to facilitate typing of reviews. This should eliminate the weeks of delay that often occurred when correcting handwritten copies.
5. Regular "status" meetings are now held to review the status of each submission, to review those on "hold," and to determine when a submission can proceed.
6. New clinical guidelines for radiopharmaceutical submissions have been proposed for the near future.
7. Two medical reviewer positions have been filled in the past three years by physicians who are board certified in nuclear medicine, in order to bring their expertise to the review process and to eliminate some of the reservations toward anything radioactive, which have been prevalent in some areas of the FDA.

The common thread through all of these initiatives is to improve communication and understanding between sponsors and the FDA, among intraagency disciplines, and among the varied levels of authority in the FDA. This improved communication should improve the review process.

The *mission* of the FDA is spelled out in the Federal Food, Drug and Cosmetic Act. The current *message* of the Agency, in general, and the Division, specifically, is that through better lines of communication inside and outside the FDA, more efficient tracking of radiopharmaceutical submissions through the system, and prompt evaluation of submissions from one level of authority to the next, we may significantly improve the review process for this class of drugs.

IMPROVING SUBMISSIONS

The sponsors of NDAs play an important part in the approval process. Submissions that are carefully prepared and include all of the required demographic, safety, and efficacy data and statistical analyses aid the review process. Protocols that are carefully constructed, so that the end points of investigation support the objectives of the clinical trials from Phase I through Phase III, help meet the FDA's legal standard of "adequate and well controlled studies." Problems sometimes arise in determining the elements of the trials that are needed to meet those standards. The Division hopes that through improved communications with the sponsors and those at all levels of new drug development, the misunderstandings and confusion that have hampered the review process in the past may be curtailed and that problems can be solved early in the process.

Time alone will tell whether the above initiatives will have the desired effect of promoting efficacy in the review of new radiopharmaceuticals. The new direction does suggest that the complaints of the medical community have been heard and that an attempt is being made to address the problems. If these initiatives are successful, they will benefit sponsors, investigators, and all of the nuclear medicine community.

REFERENCES

1. Code of Federal Regulations 21, sections 312.20–312.23.
2. *Guidelines for the clinical evaluation of radiopharmaceutical drugs.* Rockville, MD: Document Management Branch, October 1991. (Docket No. 810-0250.)
3. Johnson J, Temple R. Food and Drug Administration requirements for approval of new anticancer drugs. *Cancer Treat Rep* 1985;69:1155–1157.