The Radiopharmaceutical Approval Process: A Day in the Life

Getting a new radiopharmaceutical approved by the FDA often requires a manufacturer to jump through hoops. Why is the process so much easier in Europe?

On June 4, 1993, industry executives at Amersham mailed a new drug application (NDA) to the Food and Drug Administration (FDA) for a myocardial perfusion imaging agent called ^{99m}Tc-tetrofosmin (Myoview). Myoview works similar to Dupont's heart imaging agent, ^{99m}Tc-sestamibi (Cardiolite), but Amersham says it is faster and simpler to prepare and clears more quickly from the lung and liver (in 15 minutes versus 60 minutes), thus enabling physicians to begin imaging sooner. Two months after the NDA was filed on the scheduled deadline, the FDA informed Amersham that Myoview would be reviewed by the agency for approval. The green light for review was on the condition that Amersham perform an additional pharmacology study on dogs. The FDA set a deadline of December 4, 1993 to decide whether to approve the new imaging agent.

Thus begins the process of getting a radiopharmaceutical approved in the U.S. Although the path tends to appear short and smooth at the outset, those in the industry know that the road usually gets longer and bumpier before final approval by the FDA.

Radiopharmaceutical manufacturers cannot help comparing the sharp contrasts between the drug approval process in Europe versus America. New imaging agents tend to be approved much more quickly in Europe and are often on the market for months or even years before they are allowed into the U.S. In addition, the formation of the European Union in 1992 has made it easier to get a drug approved simultaneously in the various Western European countries. The European system is also more open to researchers who wish to conduct trials using unapproved radiopharmaceuticals.

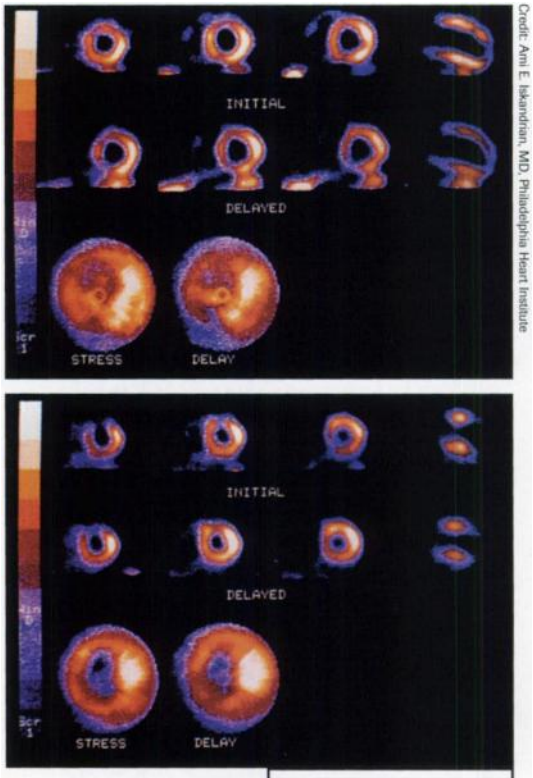
Still, some manufacturers contend that the European system—with its 15 member countries—has become a bureaucracy akin to the FDA. Overall, the system for approving new radiopharmaceuticals in both parts of the world is far from perfect. The speed of approval often depends not on the product itself but on commercial demand, the knowledge of the reviewers or just plain chance. Unfortunately, this serendipitous review process can determine whether a new imaging agent will gain widespread use in nuclear medicine. The story of Myoview's journey through an FDA review illustrates this point.

Second Generation Products Get Short Shrift

Hoping to hold the FDA to its deadline promise on Myoview, Amersham executives in charge of regulatory affairs began calling the agency in October 1993 to get them to schedule inspections at Amersham's clinical and manufacturing sites. They were told the inspections could tentatively take place in December. However, a misplaced file that contained the FDA's previous inspection of the site, coupled with a delay of transferring the inspection requests from one FDA office to another, delayed the inspection until February of the following year.

During that same fall, Myoview was approved by the European Union—only 13 months after Amersham submitted the application. By February 1994, five European countries and Japan had approved Myoview. Amersham executives say Myoview's sales abroad have been off to a good start.

One of the reasons for the delay in reviewing Myoview may be due to the fact that there is a similar product (in this case Cardiolite) already on the market. Many industry experts believe first-of-their-kind products are approved more quickly than the second or third product to come along. The

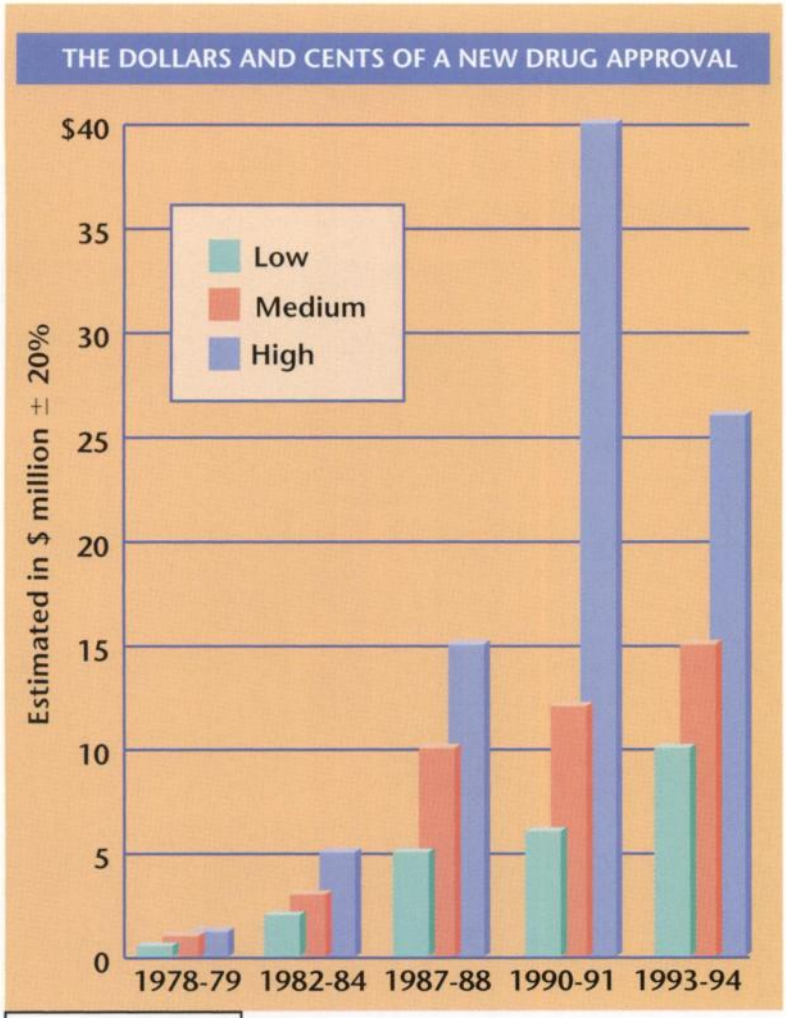


Credit: Ami E. Iskandrian, MD, Philadelphia Heart Institute

These images demonstrate (top) abnormal SPECT exercise and (bottom) resting scans using ^{99m}Tc tetrofosmin (Myoview). They are consistent with scar and ischemia in the left anterior descending artery.

FDA is often pressured to push through a first-time product, especially if it has lifesaving potential. Feeling less of a sense of urgency on the next go-around, "the agency tends to be tougher or more discerning on the 'me-too' products," said Richard A. Holmes, MD, vice president of research and development at Dupont Merck Radiopharmaceuticals in North Billerica, MA.

For instance, Cytogen submitted an NDA this past June for ^{153}Sm-EDTMP for metastatic bone pain, a product similar to Amersham's already approved ^{89}Sr (Metastron). The FDA has since requested data on breast cancer patients and on the therapeutic potential of the product in shrinking tumors even though this was not on Cytogen's NDA, according to Holmes. "The FDA is a lot more discriminating in the criteria that they want Cytogen to meet than they were for Metastron," he said. Another case in point: ^{99m}Tc-exametazime (Ceretec), which detects cerebral perfusion abnormalities in stroke victims, was approved in only 9 months compared to the me-too product, ^{99m}Tc-bicisate (Neurolite), which took around 3 to 5 years to get approval, said Holmes. Moreover, the indications on Neurolite's package insert say it can only be used after stroke has already been diagnosed, whereas Ceretec's insert has no such distinction. "Neurolite was submitted in the U.S. before it was submitted in Japan, yet it was approved several months earlier in Japan. This is despite the fact that Japan is known as the strictest country when it comes to approving radiopharmaceuticals," said Carl Seidel, MS, chairman of the Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR) and associate director of technical affairs at Dupont Merck.



The graph illustrates the increasing costs over the years of getting a single radiopharmaceutical NDA approved—from the first toxicity study to the final clinical trial.

The FDA denies that it is stricter on new drugs that are not the first of their kind. David Woodbury, MD, a medical reviewer in the department of drug imaging at the FDA, said each new drug is assessed on its own merit, and its approval time is based solely on the clinical data and NDA. As part of an effort to shorten the review process, he said FDA reviewers are beginning to work with drug companies before they begin clinical trials to ensure that the protocols meet FDA standards.

Loss of U.S. Research Dollars to Europe

A new FDA consumer safety officer was put in charge of coordinating the Myoview NDA in September 1994, which stalled the review process for a few months. In December, John Waterman, vice president of regulatory affairs/quality assurance at Amersham, sent a letter to the FDA's drug evaluation director detailing Amersham's frustration over the delays in reviewing the NDA. He received a response in January saying a final decision should be made by April 1995.

In order for a new radiopharmaceutical to be approved in the U.S., the FDA has traditionally required that some of the drug's human clinical trials be performed in this country. For example, Myoview's toxicity studies were performed in Great Britain, but its human clinical trials were conducted by both American and European researchers. The approval of ^{111}In-pentetreotide (OctreoScan)—to image neuroendocrine tumors bearing somatostatin receptors—in the spring of last year marked the first time that the FDA approved a radiopharmaceutical based on trials conducted exclusively outside the U.S. (in various European countries). Bart Doedens, MD, MBA, director of marketing at Mallinckrodt Medical, Inc. said he thinks the FDA is becoming more open toward accepting data from trials performed in foreign countries.

Although this is a plus for radiopharmaceutical manufacturers based in Europe and Japan, it has presented some problems for American researchers. "We are losing U.S. research dollars

to Europe," said Aldo Serafini, MD, a professor of radiology and medicine at the University of Miami School of Medicine who has conducted clinical trials for radiopharmaceutical companies. Corporations have a major incentive for sending their research grants abroad: For trials conducted in America, they pay researchers $1500 per patient as compared to $500 per patient for trials conducted in Europe, according to Serafini. The reason? Medical research laboratories in most European countries are funded by the government, so university professors do not need to rely on corporate grant money to support their research staff. In the U.S., research fellows and lab assistants are often hired only for the lifetime of a grant. In essence, drug companies save big money by conducting their trials in Europe because foreign governments will foot part of the bill.

As research funding is drained from American universities, researchers are finding themselves excluded from important drug trials. Take the case of OctreoScan. Serafini says his research team has tried to publish journal articles detailing the peptide's success in binding to somatostatin receptors in various types of tumors. "At the same time we submit a paper evaluating 100 patients, European researchers have submitted a paper with 300 patients," he said.

Money is not the only reason for the lag in American research. Another major consideration involves the FDA's requirements for conducting clinical trials on unapproved drugs or unapproved indications for approved drugs. The FDA requires that researchers file an investigational new drug application (IND) before beginning testing on humans. Under the European Union, however, researchers often do not need to get approval for conducting human trials under a more lenient "compassionate use" policy, which allows research to be performed on patients for lifesaving purposes.

This policy also extends to marketing, selling and distributing a drug before it is approved. Once a company has finished Phase II and III clinical trials, it can begin marketing and selling an unapproved product on a limited basis throughout

(Continued on page 30N)

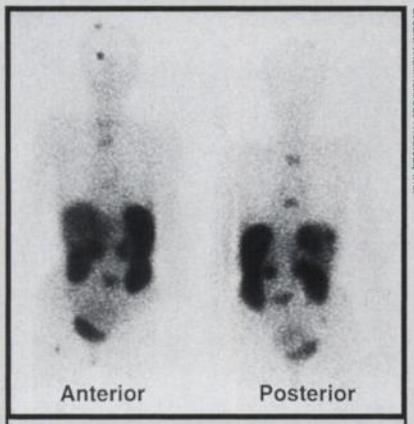
Charging Drug Companies for FDA Approval

Acknowledging that the FDA was taking too long to approve new drugs, Congress passed the Prescription Drug User Fee Act of 1992. The intention was to enable the FDA to collect user fees from pharmaceutical companies and to use the proceeds to hire 600 new drug reviewers to accelerate the review process. Indeed, the average time between submission of an NDA and final approval has dropped from 30 months to 20 months from 1992 to 1994.

On the other hand, many critics in the radiopharmaceutical industry complain that the fees are astronomical. A new drug approval application (NDA) currently costs a company $208,000 in user fees which will rise to $233,000 by 1997. If the application is rejected for review, the FDA keeps half of the $104,000 deposit. For each approved drug on the market, companies must pay an additional $12,500 per year. To have a package insert expanded costs another $104,000 in user fees. These costs may seem like pocket change for a company manufacturing a potentially large-market drug such as a new clot-dissolving agent. The costs are significant, however, for the radiopharmaceutical manufacturer whose products reach a much smaller market. The increasing costs and delays that are still present in the approval process "are discouraging radiopharmaceutical companies–especially small start-up firms–from investing in new products," said Richard A. Holmes, MD, vice president of research and development at Dupont Merck Radiopharmaceuticals in North Billerica, MA.

Under the user-fee rules, the FDA is required to review all NDAs within 12 months, but its current goal is to approve only 70% of applications within that time. Thus, applications low on the priority list still may be held up for years. Even a 6-month delay can mean thousands of dollars in lost sales. "We had hoped that new drugs would be on a faster track than they are now," said Carl Seidel, MS, chairman of the Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR) and associate director of technical affairs at Dupont Merck. "We told the FDA we didn't mind paying the user fees if we could get better results, but now we feel we aren't getting our money's worth."

One solution posed by the nuclear medicine community would be to put radiopharmaceuticals in a separate division of the FDA with a different set of regulatory requirements and a faster track to approval. "We're constantly trying to tell our colleagues that we're looking at a whole different class of drugs that have no pharmacologic effects," said David Woodbury, MD, a medical reviewer in the department of drug imaging at the FDA. While Woodbury acknowledges that a separate division of radiopharmaceuticals would make sense, he said, "we would still need to evaluate the safety and efficacy of these drugs."



Credit: Mallinckrodt Medical, Inc.

Whole-body images using the recently approved ^{111}In-pentetreotide (OctreoScan) show multiple carcinoid metastases in the brain, liver, pelvis, thoracic and lumbar vertebra, and abdomen.

Radiopharmaceutical Approval

(Continued from page 22N)

Europe. The product can be advertised in medical journals and sold to physicians and hospitals; what's more, it is usually covered by health insurance.

In comparing the approval process for OctreoScan in Europe versus the U.S., Doedens said there was little difference in terms of the reviewer's questions and the approval time (19 months in the U.S. versus 14 months in Holland). "The major difference," he said, "is that it was possible to get preapproval sales in Europe, which is not allowed in the U.S." Doedens said advanced sales of OctreoScan were a significant impetus for boosting sales once the product was approved. Even though the synthetic peptide was approved around the same time in both Europe and the U.S., its sales in this country are still lagging behind its sales abroad.

The Somewhat Disjointed European Union

In 1992, the drug approval process became centralized for members of the European Union (which includes the Western European countries such as Great Britain, France and Germany). Radiopharmaceutical manufacturers still apply to a specific country for approval—for instance Holland handles most of the NDA's for monoclonal antibodies—but the Union coordinates the approval for the rest of its member countries. Although the European Union was founded on the best intentions, "it is becoming more like the FDA with its bureaucracies and regulations," said Doedens. Once a new drug is approved by one country, the other members have an opportunity to comment on the application when it reaches the Union, which can slow down the process. What's more, the Union has set up more restrictive rules for promoting a product before it is approved.

Perhaps the largest problem has centered around trying to get 16 countries to agree to one set of regulatory laws. Some countries have traditionally taken a much tougher stance on regulating imaging agents than others. Holland and Finland, for instance, had never regulated radiopharmaceuticals as drugs before they joined the Union. Great Britain had very strict regulatory laws, and Germany went as far as to regulate PET radiopharmaceuticals, which the FDA is now considering.

For the future, the FDA is currently looking into an worldwide cooperation of sorts. It is participating in an international conference on harmonization next month in which agency representatives will meet with Asian and European drug regulatory officials, as well as technical experts in the pharmaceutical industry, to see if they can establish some common guidelines for fast-tracking drugs that have already been approved in other countries. In the meantime, products like Myoview must still go through separate review processes in order to be distributed in Europe, Japan and the U.S.

This past April, the fate of Myoview was seen as uncertain when the FDA safety officer called and said her department was still "waffling" on whether to write an approvable letter. In the meantime, Amersham executives were told they needed to answer the chemistry reviewer's questions on a degradation study and they also needed to revise Myoview's package insert.

Things started looking up in May, when Waterman and other Amersham executives received word from the FDA safety officer that an approval letter was in the works—although the letter still needed review by at least a dozen FDA officials before it could be sent. On July 14, 1995, Amersham received an official "Approvable" letter from the FDA accompanied by 10 pages of questions and a request that an additional "Phase IV" clinical study be performed after approval. On August 22, Amersham executives mailed off their response to the FDA's questions. It was more than 10,800 pages long. As of press time, Myoview still had not received official FDA approval. There will probably be a few more rounds of letters with questions and requests before the process is finished. Watterman says they're hoping for approval by the end of this year—two years after the FDA's original deadline. When Myoview will actually be approved is still anyone's guess.

Deborah Kotz

Nobel Laureates

(Continued from page 25N)

munications, he said, can allow cells to multiply wildly or disease-causing pathogens to run rampant.

Although formally retired, Rodbell continues to do research on cellular communications and has firm views on where he thinks the field is heading. "Future research will continue to focus on assessing cellular communications to show how the communications networks in similar cells are in fact very different," he said. For instance, cloned cells have been found to have different internal structures and communication networks. "We think, and hope, that people are going to follow our lead, and with the benefit of ever-improving imaging technologies, such as PET, gain better and better glimpses of the functioning of the intercellular communications grid," said Rodbell. Gilman, who currently serves as the Raymond Willie Distinguished Chair in Molecular Neuropharmacology at the University of Texas Southwestern Medical Center, is even more optimistic: "We anticipate knowing every molecule involved in G protein-mediated transmembrane signaling—all of the hundreds of receptors, G proteins and effectors. We will thus be able to decipher the complete wiring diagram for the signaling switchboard for every cell. This knowledge will have enormous implications for drug development and the rational treatment of disease."

A New Understanding of Cholesterol

Using radionuclides for their research on cellular receptors, Michael S. Brown, MD and Joseph Goldstein, MD, from the Molecular Genetics section at the University of Texas, shared the 1985 Nobel prize for their discovery of a low-density lipoprotein receptor (LDLR) and its role in familial hypercholesterolemia. "While knowledge of receptors surfaced almost 50 years ago when investigators tried to con-