FDA'S TREATMENT IND: GOOD NEWS OR BAD NEWS FOR CANCER CARE?

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Summary: *Many providers believe the FDA's new "fast track" approval process for experimental drugs—treatment IND—is a step in the right direction, but participants at a recent AMA-FDA conference raised serious questions about such issues as payment, access, liability, and the effect on clinical trials.*

The new treatment IND regulations, passed by the Food and Drug Administration in May 1987, are intended to "make promising investigational drugs available, as early as possible in the drug development process, to patients with serious or immediately life-threatening diseases," said Frank Young, M.D., commissioner of the FDA, at a February conference in Washington, DC. The conference, co-sponsored by the FDA and the American Medical Association (AMA), provided an opportunity for providers, purchasers, insurers, researchers, and other involved parties not only to learn more about the treatment IND rule, but to air their concerns about the ethical, legal, and economic issues it raises.

AMA's Dr. Sammons

FDA's Dr. Young

THE EFFECT ON CLINICAL TRIALS

A number of speakers at the conference questioned the effect treatment IND will have on controlled clinical trials. Joseph Bianchine, M.D., president, American Society for Clinical Pharmacology and Therapeutics, is satisfied that the final rule "clearly indicates that clinical trial enrollment must be adequate before a treatment IND is put in place." But John Colwell, M.D., director of research at Charleston (VA) Medical Center, points out that it is "important that an overly zealous use of treatment IND doesn't inhibit enrollment in clinical trials. The treatment IND is a positive step," he says, "as long as it doesn't interfere with the completion of those trials."

A number of conference participants, including James Sammons, M.D., executive vice-president of the AMA, expressed concern that desperately ill patients will be reluctant to participate in randomized, controlled placebo trials if potentially effective drugs are available through treatment INDs. "I am sure that strong ethical concerns about placebo controls will arise," Sammons says. And "such situations could compromise industry's ability to conduct controlled clinical trials and to assess adequately, and in a timely fashion, a drug's safety and efficacy."

Ongoing clinical trials were indeed affected when trials of AZT for AIDS' patients were begun in 1986 under an IND, according to Sandra Lehrman M.D., associate head, department of infectious diseases, Burroughs-Wellcome Co., which worked closely with the FDA to speed up the approval of AZT. "Many protocols had to be modified," Lehrman notes. "The design of placebo studies was affected by the IND," she says, and there were "delays in enrollment in other studies because of the limited supply of the drug that was available." Nevertheless, she maintains that the Treatment IND can and should be used to collect additional safety and efficacy data, not merely as a vehicle for compassionate use of a drug."

Robert Wittes, M.D., associate director of cancer therapy evaluation at the National Cancer Institute (NCI), was involved in the sponsorship of a recent treatment IND for combination therapy using two experimental drugs (Ifosfamide and Mesna) in combination with two approved drugs (Cis-Platin and Methotrexate) for the treatment of advanced, refractory germ cell carcinomas. In that case, "data supporting the validity of the IND were the same as for a new drug application (NDA), but I submit that this would not be true in all cases," he says. There are "ethical and practical dilemmas to consider when an IND does render placebo trials outdated," Wittes says.

Sammons also expresses concern that if

"treatment IND pervades earlier and earlier stages of drug development, and includes large numbers of patients, it may implicitly become more and more associated with the drug approval process. The FDA will increasingly face the situation of how to appropriately keep the data derived from the treatment IND and the drug approval process separate and distinct." He warned that if such separation does not occur, "firms may wish to sponsor, under the treatment IND, only those patients with a good prognosis," which raises the "potential for improper exclusion of patients."

Although the treatment IND can "provide for the collection of data not otherwise available," William Garnett of the department of pharmacy and pharmaceutics at the Medical College of Virginia, Richmond, is worried that a lack of controls will make it "difficult to distinguish the results of multiple versus single drugs" and, as a result, it will be harder to determine risk/benefit ratios. He also echoes Sammons' concern about the enrollment of sicker patients in treatment IND trials. Such a bias in results may prompt pharmaceutical manufacturers to withdraw drugs before they are given "a real chance," he warns.

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PATIENT ACCESS AND PAYMENT

Another issue that conference participants raised had to do with patient access to drugs approved under the treatment IND. Garnett points out that "all investigational drugs are limited in supply" and, as a result, he predicts that drug manufacturers will have to "budget the amounts delivered to individual treatment sites" and "limit the number of patients enrolled."

Payment for treatment IND drugs was an overriding concern of conference participants. If pharmaceutical firms can't absorb the costs of an experimental drug, can firms decline to provide the drug? Can society impose an obligation on manufacturers to give away their products without recovering their costs? Will insurers formulate fair payment policies for the medical costs associated with treatment? "The price of the drug isn't half the problem compared to the medical care incident with administering it," Wittes of NCI points out. Incidental medical costs such as physician visits, laboratory tests, and, in particular, inpatient hospital stays, far outweigh the cost of the drugs and, Wittes says, payment denials for such costs have been a long-standing problem with regard to clinical trials.

Abbey Meyers, executive director, National Organization for Rare Disorders, predicts that "if this new system is widely adopted, many patients will opt not to take as many tests as they should and vital information will be lost." Adoption could also lead to placebo trials that are conducted only among the lower classes of society who, because of payment barriers, cannot access the treatment IND studies, Meyers contends.

"If the system is going to be loosened," warns William Curran, a professor of legal medicine at Harvard University, "it must be available to all." At this point in time, however, Curran believes that "experimental medicine is considered a privilege," which is why subjects are not required to pay for the drugs. But if you turn the situation around and say the object of the treatment IND is not to "learn more," but to provide persons with the "benefit of the drug," subjects approach the definition of a patient and that changes the ethical questions involved in the payment question.

Although two representatives of California-based insurers (Ralph Schaffarzick, M.D., senior vice-president and medical director, Blue Shield, and G. Wilson, M.D., Medicaid), note that they would pay for experimental drugs, the coverage must be "compassionate but selective," Schaffarzick said, noting that in 1987 Medicare, the Blues, and other insurers experienced "a severe drop in actuarial reserves." Nevertheless, he said that the treatment IND "is a commendable step forward and [Blue Shield of California] will take every step to make it work for us." Wilson of the California Medicaid program noted that they have reworked their regulations governing investigational drugs and

Q & A on Treatment IND

Q: What is the purpose of treatment IND?

It has a two-fold purpose according to Joseph Levitt, executive assistant to the FDA commissioner. "First and foremost, it facilitates the availability of promising new drugs to the desperately ill as early in the drug development process as possible and, second, it allows us to obtain additional data on the drug's safety and effectiveness."

Q: Who can apply for a treatment IND?

"Individual investigators can have their own IND for a specific protocol for an investigational drug," says Robert Temple, M.D., director of the FDA's Office of Drug Evaluation. Other sponsors may include research institutions, public health departments, and, of course, pharmaceutical firms.

Q: What criteria must a drug meet?

Otis Bowen, M.D., Secretary of Health and Human Services, explains that investigational drugs approved for use outside of controlled clinical trials must meet the following criteria: the drug is intended to treat an immediately life-threatening disease (i.e., advanced cases of AIDS; metastatic, refractory cancer) or a serious disease (i.e., Alzheimer's disease, advanced multiple sclerosis); no satisfactory alternative drug or therapy exists to treat the disease in the intended patient population; the drug is or has been under investigation in a controlled clinical trial; and the sponsor of the trial is actively pursuing marketing approval of the experimental drug with due diligence.

Q: During what phase of testing can a sponsor apply?

In the case of drugs intended to treat serious diseases, "we would expect Phase III clinical trials to be fully enrolled and well underway," FDA Commissioner Young says. There must be "sufficient evidence of safety or effectiveness to support treatment use." If a drug is intended for an immediately life-threatening condition, Young says that "treatment use may be approved for agents that have not quite entered

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Q & A...

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Phase III testing, under appropriate circumstances." However, "the body of available scientific evidence must provide a reasonable basis to conclude that the drug may be effective in its proposed use or that patients receiving it will not be exposed to a significant and unreasonable additional risk of harm."

Q: Is this a significant change in FDA's approval process?

"Although the treatment IND regulations are significant and far reaching, they build fundamentally on major precedents clearly imbedded in FDA's past," says Young, the FDA Commissioner. The regulations "codify, highlight, and sharpen the focus" of the process. And, Temple of the FDA points out, "there is only one IND, but several protocols under it; treatment IND is one protocol." (Other protocols include the Compassionate IND and the Emergency IND, which have been available for some time.) But one way in which the new regulations do mark a significant change, according to Jay Plager, a former HCFA attorney who helped formulate the regulations, is that "for the first time, the burden of proof is on the government to prove why a patient should assume risk and have access to an investigational drug."

Q: What patient safeguards does the FDA require?

Both informed consent and institutional review board (IRB) review will continue to be required. However, in the case of IRB review, non-local IRB review may be an option, for instance, the use of a national IRB. Sponsors may also request an IRB waiver for a particular protocol, set of protocols, or in cases of

will now pay for "experiment treatment," so that clinical trials are now covered. However, he points out that such policy changes "will shift the research costs currently being borne by manufacturers, research universities, etc.," and pointed to the need for "adequate cost containment and utilization control mechanisms."

However, Susan Gleeson, executive director, technology management, representing the National Blue Cross and Blue Shield Association, noted that the treatment IND presents a "potential coverage dilemma," because "current contracts exclude investigational treatments that have not received final marketing approval by the FDA for coverage." She noted that the Association is still examining the issues that treatment IND raises, but potential policy changes may include coverage for outpatient treatments through Major Medical insurance supplements. "But," she said, "the big issue of who should pay for research remains."

George Rathmann, Ph.D., president and CEO of AMGEN, a biotechnology company, maintains that "what is needed is a second step by the FDA." Once the FDA completes its treatment IND deliberations, "it should declare the product licensed for that indication." If such were the case, and the drug was FDA-approved, it could have a positive impact on third-party payment.

INVOLVING COMMUNITY PHYSICIANS

A major concern of Michael Weintraub, associate professor of pharmacology and medicine at the University of Rochester, NY, is that physicians affiliated with large medical centers have an advantage in participating in treatment IND trials because of the information resources available to them through their institutions. "In contrast," he says, "community-based physicians are less likely to be aware of experimental therapy and they do not have the staff to gather needed data about the available options."

Such "roadblocks will have to be overcome," Weintraub says. To that end, he endorses a type of "regional investigator system" in which a primary investigator for a region would be supplied by the treatment IND sponsor to work with interested physicians. "A regional system would better serve the needs of patients," Weintraub says, because it would facilitate the monitoring of patient treatment, provide a centralized point for payment discussions with local payors, ensure that local patient consent processes are followed, and protect the confidentiality of data collection.

LIABILITY RISKS

The major liability risk that participating physicians may encounter as a result of the treatment IND regulations is in the area of "timely inclusion of eligible patients in available IND treatments and sufficient warning about the treatment's safety," says B. J. Anderson, associate general counsel of the AMA.

"Physicians must inform patients about treatment IND options," Anderson notes. "Physicians who fail to make a diagnosis that would put a patient in a treatment IND protocol, or do not make the diagnosis early enough to prevent a shortened life span," could be vulnerable to a law suit. As a result, Anderson emphasizes the importance of disseminating treatment IND

TREATMENT IND FOR GERM CELL CARCINOMA

FDA approval of the drugs Ifosfamide and Mesna in combination chemotherapy for advanced, refractory germ cell carcinomas was granted to the National Cancer Institute largely on the basis of clinical trials conducted at Indiana University. The treatment holds promise for an estimated 500 eligible patients per year. The studies in Indiana involved more than 50 patients who had shown drug resistance to prior chemotherapy regimens, according to Robert Wittes, M.D., associate director, Cancer Therapy Evaluation, NCI.

The principal investigator in the study, Larry Einhorn, M.D., recorded a 23 percent response rate to the four-drug combination therapy. To date, about one-third of the patients treated have had complete remissions, with a median duration of 34 months, and an additional 15 to 20 percent of patients experienced a complete remission for more than one year.

"Therapy of such unprecedented efficacy" forms the "rationale for submission of the treatment IND," Wittes explains. However, the side effects from this treatment regimen can be severe, and Wittes says that physicians who are interested in treating patients under this NCI protocol need to be "acquainted with cytotoxicity." ■

emergency use. However, sponsors must provide specific information on why IRB review is not needed, why a waiver is in the best interest of patients, and what alternative protection mechanisms will be employed. Even if a waiver is approved by the FDA, "it is up to the local institution whether or not to accept it," says Bernice Lee, a public health advisor with the FDA's Office of Health Affairs.

Q: How many applications has the FDA approved?

"There have been 12 submissions," says Commissioner Young. "Four requests have been approved, five are on clinical hold, two have been returned to the sponsor, and the remaining application is being discussed with the sponsor." The primary reason for denial, according to FDA's Temple, has been the "lack of clinical trials or the lack of active pursuit of clinical trials." Drugs must be "under current and active study" to be considered for a treatment IND, Temple says. Applications are put on clinical hold when the scientific safety and efficacy data is inconclusive. (It should be noted that the FDA cannot reveal what agents are currently under review for a treatment IND without the consent of the sponsor.)

Q: How can I obtain more information about the process?

The FDA will soon have a pamphlet available that explains the treatment IND regulations. The sponsor of a specific protocol will provide interested physicians with an "investigator's booklet," which presents specific information about the protocol. Additional information about application forms, sponsor requirements, currently approved treatment INDs, IRB requirements, etc., can be obtained by calling the FDA (Phone: 301/295-8012). Updates will also be published in upcoming issues of the *Journal of the American Medical Association* and the *FDA Drug Bulletin.* ■

approval and protocol information in a timely fashion. However, "physicians can't be sued if they don't have access to the information, and they can't be sued for not sponsoring an IND protocol. They should, however, document their attempts to enroll patients on treatment IND protocols."

HOW WILL TREATMENT IND AFFECT ONCOLOGISTS?

The AMA-FDA conference—the first public forum for examining the new regulations—raised multiple concerns, especially in the areas of clinical trials and payment. Nevertheless, participants made it clear that they approve of the intent of the new regulations—to provide a "fast track" approval process for promising experimental treatments for the desperately ill.

Emil Freireich, M.D., University of Texas, M. D. Anderson Tumor Institute, Houston, who attended the conference, believes that the treatment IND rule is "quite important, because the FDA has, for the past several years, taken the position that its concern was exclusively with safety. The consequence was that millions of cancer patients were denied access to investigative treatments, even those that were proven effective with regard to safety concerns." Freireich sees the treatment IND as "a second Renaissance for cancer research," because it's "the first time the FDA has formally recognized that patients' situations are variable and is allowing safety requirements to be superseded" by the health care needs of the desparately ill—a change that he believes will "open up the entire cancer research field."

However, David K. King, M.D., president of the ACCC, points to two concerns that he believes most clinical researchers share: the neglect of *controlled* clinical trials in favor of treatment IND trials, and the question of who will pay for treatment IND agents. Oncologists have doubts about how much of the data collected through treatment IND trials will effectively supplement the safety, efficacy, dosage, and other information requirements the FDA will continue to demand before approving a drug for marketing. And, in the area of reimbursement, King points out that "there is a provision in the treatment IND that allows for charging, on a cost basis, for treatment IND drugs. And while there are many reasons why some pharmaceutical firms, especially the larger companies, may choose not to charge for the drugs, certainly some firms will." This, according to King, will "force third-party payors to reassess their payment policies for investigational agents."

However, as King adds, "Most practicing oncologists will welcome anything that allows the provision of state-of-the-art care in a more timely fashion." And any change that can "shorten the time it currently takes for a drug's safety and efficacy to be proven to the date of its availability, especially drugs intended for the seriously ill, is good." In general, he says, "the treatment IND will force an examination of issues. Hopefully, its intent and application will prove to be of benefit to patients." On the other side of the coin, if oncologists worst fears prove true, patients may find that the latest "wonder drug" is available much more quickly but, three years after the fact, FDA marketing approval has yet to be granted and, thus, third-party payors are still denying payment. ■

Treatment IND-Approved Drugs June 22, 1987 to March 31, 1988

Drug	Indication	Sponsor
Tetrahydroaminoacridine (THA) (Approved 8/87)*	Alzheimer's disease	National Institute on Aging
Cytomegalovirus Immune Globulin (Approved 10/26/87)	Renal transplants	Massachusetts Dept. of Public Health
Ifosfamide & Mesna (Approved 1/25/88)	Germ cell carcinoma	National Cancer Institute
Trimetrexate (Approved 2/16/88)	AIDS-related pneumocystic carinii pneumonia	National Institute of Allergy and Infectious Diseases

*The FDA halted THA tests that were being done with Alzheimer's patients in October 1987, because liver enzymes rose abnormally—a possible symptom of liver disease. However, dosages were adjusted, and trials resumed on February 3, 1988.