POLICY QUESTIONS CONTINUE TO SURROUND TREATMENT IND

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On March 19, 1987, the Food and Drug Administration (FDA), proposed regulations under which investigational drugs and biologics might be made available for treatment outside of the clinical trial setting. The final rule on treatment use and sale was published in the *Federal Register* on May 22, 1987.[1] These regulations, which went into effect the following month, represent a formalization of a process that the FDA has previously employed for some drugs prior to final marketing approval.

In the past, drugs undergoing clinical trials under an Investigational New Drug (IND) exemption have been made available outside of trials when early clinical evidence appeared strongly favorable. For example, nifedipine and verapamil (calcium channel blockers), and zidovudine (AZT) were all granted treatment status prior to final FDA marketing approval. In fact, 20,000 patients were treated with nifedipine, 5,000 with verapamil, and 4,000 with zidovudine prior to marketing approval of their New Drug Application (NDA).[2]

The treatment IND regulations specify circumstances under which the FDA will consider a request to make an investigational compound available for patient treatment outside of a controlled trial. However, such requests must meet the following criteria:

- The drug is intended to treat a serious or immediately life-threatening disease.
- There is no comparable or satisfactory alternative drug or other therapy to treat the intended population's stage of disease.
- The drug is under investigation in a controlled trial under an IND, or all clinical trials have been completed.
- The sponsor of the controlled clinical trial is actively pursuing marketing approval of the drug with "due diligence."

The FDA Commissioner may deny a request for a treatment IND if available scientific evidence fails to provide a reasonable basis for concluding that the drug may be effective for its intended patient population, or if a drug may expose patients to an unreasonable and significant additional risk of illness or injury.

The FDA's definition of an immediately life-threatening disease is one "in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment." Examples cited in the *Federal Register* of immediately life-threatening diseases include "most advanced metastatic refractory cancers." Examples of serious diseases include "advanced multiple sclerosis" and "transient ischemic attacks."

Treatment protocols for IND drugs may be submitted to the FDA by the sponsor of the drug. A licensed medical practitioner may also submit a treatment IND to the FDA if the sponsor of a drug is unwilling to establish a treatment protocol under the IND regulations.

A more controversial section of the new regulations permits sponsors to charge for the investigational drug provided under a treatment IND if there is adequate enrollment in its ongoing clinical investigations. However, such charges are not permissible without prior written notification of the FDA, and the sponsor may not commercialize an investigational drug by charging prices greater than those required to cover its manufacturing, research, development, and handling costs.

KUDOS AND BRICKBATS: RESPONSES TO THE PROPOSAL

The FDA received a great many comments following publication of the initial treatment IND proposals. The vast majority of medical professionals were supportive of the concept of making available "breakthrough drugs to desperately ill patients when no other alternative therapy exists."[2] The FDA concluded that the comments it received reflected a "broad public support" for its initiative to provide promising new drugs to very ill patients "as early in the drug development process as possible."[1] At the same time, however, serious concerns were expressed about the exposure of patients to potentially untested drugs, how the new rules might affect the drug development process, the potential for delay in final drug approval, and the sale of investigational drugs with the attendant issues of equity, reimbursement, etc.

The FDA decided that such concerns were of significant merit and, as a result, changes were incorporated into the final treatment IND rules that both support the goals of the initial proposals and reduce the possibility of abuse. The final rules included such elements as a definition of what constitutes an "immediately life-threatening" disease, the need for compliance with informed consent and institutional review board regulations, and clarification of the requirement for sufficient scientific evidence to permit reasonable judgments about a drug's efficacy and the potential exposure of patients to undue risk.

CLINICAL TRIALS AND TREATMENT IND

A recent editorial in the *Journal of the National Cancer Institute*[3] raised the issue of the treatment IND's potential negative

effect on the drug approval process.

Although the potential for delaying marketing approval is of legitimate concern, many of the arguments presented in this editorial were less than substantive. For example, the author proposed that the availability of drugs outside of clinical trials might diminish both physicians' and patients' enthusiasm for participating in such trials. Although the author admitted that there was little data to support or reject such a view, he equated the treatment IND's potential for evoking such a response with NCI's experience with Group C cancer drugs, pointing out that only one of the three drugs placed in Group C since December 1977 (etoposide) has been approved.

However, the other two drugs in question are either generally considered to be of somewhat limited clinical utility (amsacrine [mAMSA]) or are quite novel, have not yet been widely studied outside the NCI, and require complex procedures in conjunction with drug administration (IL2/LAK cell therapy). In fact, the NCI placed IL2/LAK cell therapy in a separate, modified Group C category and restricted its use to comprehensive cancer centers.

Several other questions concerning the effect of treatment INDs on clinical trial enrollment were raised during the joint American Medical Association (AMA) and FDA conference earlier this year. Although these issues were summarized in the Spring issue of this *Journal* ("FDA's Treatment IND: Good News or Bad News For Cancer Care"), some specific concerns need to be addressed, particularly as they might apply to cancer centers.

For instance, some conference participants suggested that patients would be reluctant to participate in randomized, placebo-controlled trials if potentially effective drugs were made available under the new treatment IND regulations. However, for the cancer patient population, the proportion of clinical trials using placebo controls is quite small; of 333 phase III protocols listed in the National Library of Medicine's PDQ database, only one study (EORT-40861) employs a placebo control arm.

Other issues, such as selective enrollment of patients under treatment rules, overzealous use of the treatment IND designation, and perception of the treatment IND status as synonomous with drug approval, do not relate to the new regulations themselves, but to how they are applied by the FDA in particular circumstances. At present, the data simply are not available to address those points. Over time, observation will either lay those fears to rest or necessitate a restructuring of the process.

THE PAYMENT QUANDARY

The issue of charging for investigational therapies is more problematic. A proponent of so-called "patient funded research" wrote in the *New England Journal of Medicine* that this action by the FDA "confirmed the validity" of his institute's position (i.e., that it is appropriate to charge patients for investigational therapies).[4] Although, to my knowledge, this analogy has not been further pursued in the medical literature, the author's comparison between the new regulations and his own viewpoint is disturbing, because the concept of patient-funded research is opposed by many medical professionals.[5,6,7] It it also at distinct variance with the attitude of some leaders within the medical community. For instance, the editor of the *New England Journal* appeared on national television to express his disapproval of such a practice.

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There is little doubt that if patients are required to personally bear the costs for investigational drugs, the opportunity to receive such therapy will not be equally available to all. The FDA has pointed out that although the opportunity to charge for both investigational drugs and medical devices has existed in regulations since 1963 and 1980 respectively, no significant problems have arisen in the past. In addition, the Agency has noted that disallowing cost recovery when drug sponsors consider it necessary may mean that no patients receive such therapy. However, this position seems unlikely to mollify the criticisms of those who emphasize that patients must have equal access to new therapies.

Reimbursement for charges assessed under a treatment IND is another unresolved issue. Although the public assumes that its insurance carriers will reimburse for the costs of medical care, few insurers will pay for investigational treatments. An excellent review of this issue has been published.[8]

The authors point out that although such an exclusion is part of carriers' insurance contracts, some courts have held that particular treatments may be experimental, yet at the same time, be considered reasonable and necessary, because they are the best treatments available for those patients. The authors conclude, however, that insurers probably do not have to pay for treatments that the new regulations suggest are appropriate options for certain patients because, in effect, to require such reimbursement forces insurers to support research for which they have not made actuarial provisions. Nevertheless, the authors do not doubt that the new treatment IND rules will increase litigation for such reimbursement.

At present, the Health Care Financing Administration (HCFA) does not cover the costs of any investigational drug, biologic, or medical device. The sole exception is the coverage of Group C cancer drugs distributed by the NCI through a joint NCI/FDA agreement. However, a logical case for such reimbursement might have been made for cytomegalovirus immune globulin (CMV-Ig), which was granted treatment IND status in October 1987. CMV-Ig is used to treat eligible end-stage renal disease patients who are undergoing transplants—a population of patients that is, by statute, already eligible for Medicare. Furthermore, profit motives are not of concern, because the producer and sponsor of the treatment IND is the Massachusetts Department of Public Health. Finally, the use of CMV-Ig is likely to result in overall lower expenditures because the cost of successful renal transplantation is less than that of long-term dialysis.

Moreover, in attempting to prevent cytomegalovirus infection in transplant recipients, the medical community often employs intravenous immune globulin—a marketed drug. Because the antibody titer to the virus in this product is considerably lower than that in CMV-Ig, a much greater quantity must be administered, resulting in a higher cost. This particular reimbursement issue is moot, however, because marketing approval for CMV-IG is imminent. Nevertheless, health professionals might view this biological as an example of the logic of petitioning for reimbursement on a case-by-case basis for treatment INDs.

It should be noted, however, that HCFA will pay for a hospital admission during which an investigational drug is given, if that admission was not solely for the pur-

pose of administering such a drug. Take, for instance, the case of a relapsed leukemia patient who is admitted to a hospital and, during that admission, treated with an investigational agent. If it is determined that the patient's medical condition necessitated the admission, the admission is covered.

TREATMENT IND'S IMPACT ON CANCER PROGRAMS

What is the potential impact of the new treatment IND regulations on a community cancer program? We can clearly all agree that the diseases such a center treats on a daily basis are indeed "immediately life-threatening." A significant percentage of a cancer program's patients might logically be considered as individuals for whom no satisfactory alternative therapy is available to treat their particular stage of disease. In short, cancer programs have patient populations that are particularly likely to utilize available new drugs or biologicals under a treatment IND. That having been said, it is nonetheless true that currently such a situation is potential rather than actual.

At the present time, only three treatment INDs are in effect. The products concerned are CMV-Ig, trimetrexate, and ifosfamide. CMV-Ig, as described above, is approved for treatment use in renal transplant recipients who are CMV seronegative and who have received a renal transplant from a seropositive or indeterminant donor.

Trimetrexate, with leucovorin rescue, is approved for treatment use in HIV positive patients (by ELISA, HIV culture, or p24 antigenemia) who have documented pneumocystis carinii pneumonia, and who have demonstrated serious intolerance to both pentamidine and trimethoprim/sulfamethoxazole. Ifosfamide has received treatment approval for use with Mesna in combination with cis-platinum and VP-16 or vinblastine in patients with refractory germ cell carcinoma.

Although there are several treatment IND applications currently under review, it does not appear likely that a large number of antineoplastic agents will be approved for treatment use in the immediate future. Drug sponsors may perceive possible disadvantages in applying for treatment IND status.

As yet, it has not been determined if treatment use will increase the liability of a treatment IND sponsor. Unanticipated toxicities that are seen in the treatment group, but not in the clinical trial group, could complicate the approval process. Furthermore, if the sponsor chooses to charge for the drug, and the eventual charges after final approval differ—which is likely—they are at risk of being perceived as having taken advantage of either patient population: the users under the treatment IND or the users after marketing approval. (Parenthetically, it is interesting to note that the manufacturers of trimetrexate and ifosfamide are providing the drug without charge.)

As a result, although the new regulations, which make investigational drugs more widely available under treatment protocols, could conceivably have a significant impact on cancer programs—analagous to the impact of the treatment use of AZT at institutions emphasizing treatment for AIDS—the magnitude of the effect is still unclear.

Cancer programs should seriously consider the ramifications of the treatment IND regulations and determine whether or not they have a unique role to play in this area. Cancer programs' leadership in addressing issues of availability, equity in distribution, and the difficult questions of reimbursement for novel cancer therapies will benefit medical professionals and patients alike.

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Although the use of investigational drugs for treatment outside of clinical trials has been possible in the past, the treatment IND regulations provide a formal avenue that may increase the availability of promising drugs to those cancer patients for whom few reasonable alternatives are possible. This could result in greater opportunities to utilize therapies for which there is evidence of effectiveness and acceptable safety, and an improved understanding of the clinical utility of a compound at the time of final marketing approval.

Finally, a considerable moral and social benefit might accrue from an increase in reasonable treatment options for patients who have advanced disease. Upon occasion, such patients conclude that medical science has little further to offer them and, in frustration and desperation, turn to the providers of "alternative" cancer remedies. It has been suggested that health professionals have an ethical imperative to discourage such behavior and to encourage patients to attempt enrollment in clinical treatment studies for which there is some scientifically-based expectation of possible benefit.[9] The new FDA regulations may serve to remind us that it is never true that there is nothing more that can be done for a patient. ■

ACS Sponsors Nursing Conference

The 21st Annual Great Lakes Cancer Nursing Conference, sponsored by the Michigan Division of the American Cancer Society (ACS), will be held on October 18-19 at the Clarion Hotel in Lansing, MI.

The two-day program, entitled "Oncology Nursing and Cancer Treatment: Coming of Age," will focus on current clinical practice and treatment issues of concern to oncology nurses. Application for continuing education credit has been made to both the Michigan and the National Nurses Associations, as well as the National Association for Practical Nurses.

For further information, contact: The American Cancer Society, Michigan Division, Inc., Director of Professional Education, 1205 E. Saginaw St., Lansing, MI 48906. Phone: 517/371-2920.

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