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Commentary

Treating Seriously Ill Patients with Experimental Drugs

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In 1987 the Food and Drug Administration promulgated the final regulations relating to the IND rewrite. These regulations, among other things, provided for the establishment of a Treatment IND. This was prompted by a number of considerations including the continual controversy over the "drug lag," essentially impeding certain important therapies from being used in a formal fashion for treatment of life-threatening or serious illness. In addition, the nation was rocked by the emergence and proliferation of the AIDS virus, responsible for a certainly fatal illness. By the time viable treatments for AIDS or other life-threatening or serious illnesses could be released from their clinical trials under an approved NDA, many patients who would not have had access to effective alternative therapies would have expired.

The Treatment IND is a political tightrope for the Food and Drug Administration (FDA). It perceived the need to release some of these drugs to desperately ill patients who would qualify but, at the same time, recognized that the drug approval process would not have run its course and that serious drug misadventures could occur as a result.

In promulgating the Treatment IND regulations, FDA wished to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible and before the beginning of general marketing. In addition, the agency desires to obtain additional data on a drug's safety and effectiveness, even though patients who might receive drugs under a Treatment IND would not be enrolled in a controlled clinical trial.

In order to qualify for a Treatment IND, a drug must be under investigation under a regular IND and the sponsor must be actively pursuing marketing approval with "due diligence." The indications for treatment use must be the same as or similar to those under study in a controlled clinical trial. Thus, unless a sponsor is pursuing a regular IND for marketing approval for a specific indication, that drug may not be released to a patient under a Treatment IND for a different indication. In passing the Food, Drug and Cosmetic Act, Congress specifically intended not to interfere with the practice of medicine. Hence, under our system of medical care, a physician is free to prescribe a marketed drug for any reason he or she wishes without violating the federal Food, Drug and Cosmetic Act. The tort system, i.e., medical malpractice system, serves as a check on the physician's practice behavior. Under the Treatment IND, the physician would be unable to obtain the drug for his patient unless he was willing to restrict its use to the indication under study in a regular IND.

In deciding whether to deny a Treatment IND application, the agency does make a distinction between serious disease and immediate life-threatening disease. With regard to serious disease, FDA may deny a Treatment IND if there is insufficient evidence of the drug's safety and effectiveness. Thus, even though the drug in question may be under an IND, unless the agency is satisfied that there is some reasonable evidence of safety and effectiveness, it will not allow the Treatment IND to proceed. However, with immediate life-threatening illness, the situation changes. FDA may deny the Treatment IND if the available evidence fails to support that the drug may be effective for its intended use in its intended population or would not expose patients to unreasonable and significant additional risks. Thus, the criteria for denial of a Treatment IND are much less stringent where immediate life-threatening illness is involved.

Even the regular IND phases during which a Treatment IND may be allowed to proceed can differ depending upon the severity of the illness. For a serious disease, for example, the Treatment IND would be allowed to proceed ordinarily during phase III or after completion of the clinical trials. Remember, a substantial amount of time would elapse between the completion of clinical trials and the ultimate approval of a new drug application. In appropriate circumstances, FDA may allow a Treatment IND for a serious disease to proceed during phase II. However, this has not yet occurred. For immediate life-threatening illness, the agency may allow a Treatment IND to proceed earlier than phase III, but ordinarily not earlier than phase II. It is more likely that a Treatment IND would be allowed to proceed during phase II for an immediate life-threatening illness than for a serious disease. In fact, at least one has been allowed to proceed during phase II and this is dideoxyinosine (DDI), manufactured by Bristol Meyers. This particular drug is used to treat AIDS or AIDS-related complex when the patient is intolerant to AZT.

The regulations spell out in detail the requirements of a treatment protocol. Included in these requirements is a list of what available regimen should be tried before using the drug or why this drug is preferable to available marketed treatments. Obviously, the agency does not wish to encourage the indiscriminate use of drugs when there are alternative therapies available. Thus, it is incumbent upon the sponsor to document that alternatives have been tried and failed or that they are not available.

Thus far all treatment INDs allowed to proceed have been sponsored by industry or government. A licensed practitioner may wish to obtain an investigational drug which is

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in controlled clinical trials for treatment use and may submit a treatment IND directly to the agency. However, that practitioner is not free to obtain that drug unless the sponsor of the clinical trials wishes to release it to him. In fact, a licensed practitioner must first attempt to obtain the drug from the sponsor of a clinical trial under a treatment protocol. Otherwise he may seek to obtain the drug from the sponsor and submit a treatment IND directly to FDA.

Whether a treatment IND is sponsored by a licensed practitioner or industry or government, patients are entitled to specific protections under the regulations. Informed consent is probably the most important of these protections. The question does arise, however, as to whether this is truly an informed consent. Opponents of the Treatment IND would argue that the patient is confronted with little choice but to take advantage of the drug if he or she wishes to live. However, even in these circumstances, the decision ultimately resides with the patient.

Other opponents of the Treatment IND concept would argue that the regulations are merely a mechanism to allow a company to derive unreasonable profits by charging for the drug under the Treatment IND. The regulations do allow for an applicant to charge for the drug. FDA must be notified 30 days before commencement of sale, but if FDA does not object, the applicant may then charge. Normally, under a regular IND, FDA must give positive approval. Thus far, however, charges are incurred with only 3 of 18 Treatment INDs.

In 1987 only two Treatment INDs were allowed to proceed. But, by early 1990 this total had risen to 18. Ten of the 18 allowed to proceed were sponsored by drug companies. In addition, while the Treatment INDs are for a variety of illnesses, 6 of the 18 were for AIDS or AIDS-related illnesses.

Companies and government agencies which are sponsoring research on drugs to treat serious or life-threatening illness can now avoid some of the frustration of not being able to treat a sufficient number of needy patients until the lengthy drug approval process has run its course. These companies or agencies must also realize that there is an even greater responsibility to pursue their clinical trials diligently to document the safety and effectiveness of these products and minimize any potential harm to patients before the product has actually been approved for marketing by the FDA. This is a difficult task given the types of drugs involved and the demand for them. If a company fails to pursue its clinical trials with due diligence, the agency may put the Treatment IND on a clinical hold. This has not yet occurred, primarily for public policy reasons. However, while the agency wishes to release these drugs to patients with serious or life-threatening illness, it does not want to see the use of the drug perpetuated under a Treatment IND.

The Treatment IND represents a major departure from the normal mechanism of drug approval in this country. It is a bold experiment, one whose success is encouraged by all parties concerned.