Noninvestigational Uses of Investigational Drugs: Some Implications of FDA's Revised Regulations

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At some point in the clinical testing of a new investigational agent, evidence of therapeutic activity may emerge. At some later point, but before evidence is sufficient to support a definitive claim of efficacy and approval by the Food and Drug Administration (FDA) for marketing, clinical investigators or the sponsor may conclude that the new agent is useful for treatment of a particular disease. This leads immediately to the question of whether the sponsor should make the agent available for treatment outside the setting of a clinical trial. The question is especially pressing if the disease commonly has a fatal outcome and lacks adequate alternative therapy and if the drug has significant toxic effects.

In past years advanced cancer has probably been the most familiar backdrop for the playing out of this dilemma. Since 1976 the National Cancer Institute (NCI) has made certain investigational drugs available outside clinical trials under its Group C mechanism, which in effect is a treatment Investigational New Drug (IND) exemption category for a particular drug and a specific cancer indication. With FDA concurrence, experimental agents may be placed into Group C if they are "drugs supported by evidence of reproducible relative efficacy in a tumor type, which alter the pattern of care of the disease, and which are safely administered by properly trained physicians without requiring specialized supportive care facilities, as judged by available abstracts, papers, and reports in the IND (L)." Drugs in Group C may be provided by the NCI to any licensed physician wishing to treat a patient with the disease for which the agent has received Group C designation. Physicians using drugs under Group C have had no reporting requirements to the NCI other than the obligation to report adverse drug reactions. Over the past 11 years this mechanism has enabled the NCI to make 14 new agents available to the oncology community for treatment purposes before marketing approval (table 1).

For active investigational agents not meeting the criteria for Group C, the NCI may still provide drugs on a compassionate basis to requesting physicians for patients whose best medical interests require them. These decisions are made on a case-by-case basis, often after discussion between the requesting physician and the NCI staff. Over the past few years criteria for releasing drugs by this mechanism have become somewhat stricter as evidence has accumulated that: (a) many patients for whom compassionate drug is requested can instead be routed to high-priority clinical trials by NCI staff; and (b) the rate of significant adverse drug reactions seems higher with this category of distribution than for the same drugs on clinical trials (data submitted for publication). We have, therefore, established guidelines for the compassionate use of each anticancer agent under NCI sponsorship; these are revised as new information emerges. Through this mechanism drugs are provided at an earlier stage of development than they are in Group C, and data supporting efficacy, though reasonably persuasive, are less well established than for Group C. For these reasons, physicians are asked to provide a medical summary of the effects of the treatment on the patient, including response and toxicity information.

The deep public alarm surrounding the AIDS epidemic has given provision of new agents for treatment particular urgency. Some AIDS patients and support groups have demanded access to experimental agents in very early stages of development, irrespective of the quality or quantity of the evidence supporting efficacy. Up to now, federal regulators have been unwilling to permit distribution of substances for which the evidence supporting efficacy is either weak or nonexistent. On the other hand, when evidence for effectiveness is at hand, the government's response has been very rapid. Unblinding of the results of the multicenter trial comparing azidothymidine (AZT) with placebo led quickly to the establishment of a treatment IND, so that patients with AIDS and a history of Pneumocystis carinii pneumonia (the subset of patients for which the clinical trial provided evidence of benefit) might have access to potentially lifesaving treatment. During the interval between establishment of the treatment IND and marketing approval of AZT by the FDA, more than 5,000 patients were treated under this mechanism.

The AIDS epidemic has motivated much public comment about the adequacy of the government's response to this daunting public health challenge. Many have accused the FDA of over-regulating the clinical drug testing process and the access of patients to investigational treatment. Although such criticisms are not new, they have found particular resonance in an administration that regards the lessening of governmental regulation in general as a political priority.

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2 Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD 20892.
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Table 1. History of Group C use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group C</th>
<th>NDA approval</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomustine</td>
<td>4/76</td>
<td>10/76</td>
<td>7/83</td>
</tr>
<tr>
<td>Carmustine</td>
<td>4/76</td>
<td>5/77</td>
<td>—</td>
</tr>
<tr>
<td>Semustine</td>
<td>8/76</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Daunorubicin</td>
<td>8/76</td>
<td>5/80</td>
<td>—</td>
</tr>
<tr>
<td>Asparaginase (Escherichia coli)</td>
<td>10/76</td>
<td>4/78</td>
<td>—</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>7/77</td>
<td>12/78</td>
<td>—</td>
</tr>
<tr>
<td>Streptozocin</td>
<td>8/76</td>
<td>1982</td>
<td>—</td>
</tr>
<tr>
<td>5-Azacitidine</td>
<td>8/76</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Asparaginase (Erwinia)</td>
<td>2/78</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hexamethylmelamine</td>
<td>7/77</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Etoposide</td>
<td>5/78</td>
<td>10/83</td>
<td>—</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>12/81</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>THC</td>
<td>10/80</td>
<td>5/86</td>
<td>—</td>
</tr>
<tr>
<td>IL2/LAK*</td>
<td>5/87</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Distribution limited to comprehensive and clinical cancer centers.

In part as a response to these pressures and in part because of its own concern with this issue, the FDA last spring proposed revisions of its regulations governing the provision of experimental agents for severe or life-threatening illnesses (2). This reproposal (the document was actually a major modification of a previous proposal) provided for radically liberalized access to investigational agents. Although the goal of providing effective drugs to desperately ill patients was widely supported, the reproposal was heavily criticized on various grounds by drug sponsors, investigators, consumer groups, and certain members of Congress. Many were particularly concerned about the lack of any requirement of efficacy for the life-threatening diseases and the possible damage to clinical research and to patient safety that might accompany the wide use of investigational agents at inappropriately early stages of development. Taking many of these criticisms into consideration, the FDA released a substantially altered “final rule” in June 1987 (3).

The essential features of the new regulations are as follows (3):

A. Treatment Use
1. “FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:
   a. the drug is intended to treat a serious or immediately life-threatening disease;
   b. there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
   c. the drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
   d. the sponsor of the controlled clinical trial is actively pursuing marketing approval with due diligence.”

2. The FDA may deny such a request:
   a. for a serious disease, “if there is insufficient evidence of safety and effectiveness to support such use”;
   b. for an immediately life-threatening disease (i.e., “a stage of a disease in which there is a reasonable likelihood that deaths will occur within a matter of months or in which premature death is likely without early treatment”), “if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:
      i. may be effective for its intended use in its intended patient population; or
      ii. would not expose the patients to whom the drug is to be administered to an unreasonable and significant risk of illness or injury.”

B. Charging for and Commercialization of Investigational Drugs
1. “Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary for the sponsor to undertake or continue the clinical trial . . .”

2. “A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided:
   a. there is adequate enrollment in the ongoing clinical investigations under the authorized IND;
   b. charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
   c. the drug is not being commercially promoted or advertised; and
   d. the sponsor is actively pursuing marketing approval with due diligence.”

3. “The sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.”

Additional provisions in the regulations stipulate requirements for the treatment IND submission and describe conditions under which the FDA can impose a clinical hold on or request modification of a treatment IND. A major source of difficulty in trying to assess the likely impact of these regulations stems from their purposeful imprecision. The wording of the basis for denial of an applica-
tion for immediately life-threatening diseases, for example, is masterfully vague; a proposal may be denied if "the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug may be effective" (emphasis added). Obviously the intent here is to leave as much uncodified as possible, so that FDA staff will retain maximum flexibility. The result is that what the FDA does with a particular treatment IND proposal will probably have more to do with the agency's prevailing philosophy at that point in time than with anything specified in regulation.

Of course, these regulations will have no impact at all unless sponsors decide to take advantage of their provisions. Whether sponsors are likely to do so in any particular case will be determined by several complex sets of considerations: (a) the estimated impact of wide availability on the pivotal clinical trials essential for eventual marketing approval; (b) desire to pursue cost recovery by charging for the investigational drug distributed under the treatment IND; (c) regulatory requirements for the clinical data accumulated under treatment IND distribution; (d) other possible business advantages of treatment IND distribution; and (e) willingness of third-party carriers to reimburse the cost of these still-investigational agents distributed under a treatment IND.

Let us consider these points individually.

Impact on orderly clinical development. No sane sponsor would wish to jeopardize the acquisition of the critical information upon which eventual FDA approval depends. For each targeted indication, therefore, sponsors can be expected to take great care that the filing of a treatment IND does not imperil timely completion of its pivotal clinical trials.

This issue is obviously a major and appropriate concern. It is not that the welfare of individual patients should be held hostage to clinical trials, but rather that an orderly clinical trials process is what determines efficacy, not the anecdotal experience by physicians outside organized research. If physicians have unrestricted access to investigational agents for treatment purposes, however, some of the motivation that currently impels the less committed ones to participate in multicenter trials may well be blunted. Also, if patients have access to investigational agents for treatment purposes, why should they be motivated to enter clinical trials? These considerations lead to the fear that premature establishment of a treatment IND may diminish accrual to key clinical trials.

Firm data on this point are hard to come by. Of the 12 anticancer cytotoxic agents placed into Group C by the NCI, 7 have found their way to market (table 1). Of these 7 agents, 6 were among the 9 that were placed into Group C within 15 months of its creation; 4 of those 6 marketing approvals were made before the end of 1978. For the 7 cytotoxic agents eventually reaching the market, the median time from Group C approval to marketing approval was 18 months (range, 6-65). It seems clear that, given the FDA approval criteria in the mid to late 1970s, the agents placed into Group C in 1976-1977 were close to marketing approval at the time of Group C approval.

As the sands began to shift, however, and the FDA moved away from response rate and toward survival and quality of life as primary endpoints, things became more difficult. Of the 3 cytotoxic agents placed into Group C since December 1977, only etoposide has thus far reached the market. Although firm conclusions are not possible, it seems altogether more likely that the long delays in marketing approval for some of the agents in table 1 relate primarily to difficulties in fitting FDA approval requirements to the needs of antineoplastic agents (4), rather than to decreased accrual onto pivotal trials as a result of treatment IND distribution.

Another related potential pitfall is that the uncontrolled use of potentially toxic agents by licensed physicians who may have no particular expertise with such agents may well be accompanied by a high adverse reaction rate. Aside from the implications for patient welfare, such a state of affairs may dampen the enthusiasm of the oncology community for systematic study of the agent in a research setting or for its use in the postmarketing period. The experience with pentostatin and mitoguazone illustrates how toxicity in early clinical trials can set back the development of particular new agents for years.

Cost to the sponsor. The establishment and administration of a treatment IND require a substantial commitment of resources. The regulations permit the sponsor cost recovery by charging for the drug. It remains to be seen whether companies will take advantage of this provision. Unless the drug is very expensive to produce, they may be reluctant to impose a charge, since the company might thereby reveal more than it may care to about its profit margin in the postmarketing period.

Monitoring and reporting requirements. The revised regulations say nothing about these critical practical issues. If the monitoring requirement for a drug distributed under a treatment IND is very lax and commercial sponsors are not required to report the experience, then a firm might well decide to favor distribution of an agent under this mechanism as long as it can, particularly since it will be allowed to charge. This is especially true of agents for which the demonstration of efficacy proves difficult. Thus a situation may arise in which drug companies might expend little effort on pivotal trials unless they are almost certain to be positive and/or not very expensive. A number of antineoplastic agents that have been long in clinical development (e.g., ifosfamide, high-dose methotrexate, teniposide, and the parenteral formulation of melphalan) might well have fallen into this category in past years.

On the other hand, if the regulatory requirements for monitoring a treatment IND are burdensome to drug companies, they will be loathe to utilize the option at all. In fact, if they are required to report these clinical details in their eventual marketing application to the FDA, they may have to make a decision whether to go for approval or stay with perpetual distribution under a treatment IND, at least until the FDA discovers they are not pursuing marketing approval "with due diligence." They may simply not be able to do both.

Assessment of potential business advantages of a treatment IND. Under some circumstances, the new regulations may actually create an incentive for companies to distribute some agents under a treatment IND as early as possible, particularly if they can charge for the drug. This is especially true for biological agents, where the proliferation of essentially
similar cloned products from many companies may motivate attempts to capture market share and generate product loyalty even before FDA approval. A similar situation may exist if several companies are simultaneously developing chemically different but clinically similar analogs of an established active drug.

Stance of third-party carriers. At present, the Medicare regulations of the Health Care Financing Administration call for reimbursing the costs of care while patients receive drugs classified as Group C. Nongovernmental insurance companies have no such policy. Many are no doubt preparing to assess the effects of the new treatment IND regulation on their costs. If they decline to pay for claims resulting from the use of experimental drugs distributed under a treatment IND, it is unlikely that the mechanism will be extensively employed. The converse may also be true: agreement to pay may be a potent stimulus to use the mechanism, since payment for the cost of care in clinical trials would probably be a functional by-product. Finally, in this era of cost consciousness, extensive attempts by sponsors or physicians to use the mechanism might produce a reciprocal backlash by third-party carriers, as they attempt to contain rising costs.

It seems quite likely, therefore, that sponsors will use these regulations more or less according to their estimated effects on company bottom lines. For these reasons, some additional implications of the regulations relating to the charge provisions are worth pondering. First, despite the explicit prohibition in the regulations, it is naive to think that commercialization of investigational agents will not occur. As things stand now, companies do this already in many ingenious ways. For marketed drugs they sponsor meetings that, though nominally educational, are really thinly veiled advertisements for unapproved indications. At the cancer meetings last spring, for example, one pharmaceutical company sponsored an "educational symposium" at which physicians were paid $100 to walk in the door. Another company regularly runs advertisements in medical journals promoting "bleomycin-containing combination chemotherapy" for head and neck cancer. It is perhaps not irrelevant that all these combinations also contain cisplatin, which cannot be explicitly advertised for this indication but whose profit potential is very much greater than bleomycin's. Under the new regulations these kinds of promotional activities will probably proliferate for investigational agents as well.

Second, as with the regulatory and monitoring requirements noted previously, the charge provisions may create a disincentive for commercial sponsors to pursue particularly problematic agents. Why should a company bother with the systematic development of a difficult (but potentially useful) agent if it can, in effect, "market" it under a treatment IND without systematic study? Although the regulations explicitly forbid charging a price that exceeds the cost to the company, seasoned company accountants who know something about the preparation of balance sheets will be able to produce ample justification for almost any price.

Despite these imponderables the revised regulations present a viable scaffold upon which sponsors, investigators, and the FDA can construct an intelligent approach toward the provision of new agents for the noninvestigational treatment of very ill people. For the NCI's drug development program, whose only bottom line is the lessening of morbidity and mortality from neoplastic disease, most of the business considerations discussed here are not directly relevant, except insofar as they affect the decisions of our industrial collaborators. We plan, therefore, to establish treatment INDS for agents whose efficacy is strongly supported by available clinical data, provided that we are reasonably sure that doing so will not compromise the clinical trials upon which final judgments of safety and efficacy depend. We shall do this at the same time that we aggressively attempt to expand the NCI-supported clinical trials network, so that increasing numbers of interested physicians will be able to participate in studies of the highest priority. This approach should help ensure the availability of state-of-the-art care to the greatest number of people, even as the health of the clinical trials enterprise itself is fostered.

Finally, it is undeniable that, whether one is talking about cancer, AIDS, or some other potentially fatal disease, the matter of treatment INDS would be much less pressing if the FDA's whole process of approving drugs for marketing were maximally fast and efficient. We refer here both to the review process itself and to the criteria by which safety and efficacy are judged in the review (4). The FDA should undertake a thorough review of the whole process by which new drug applications and biological licensing applications are evaluated, along with a scientific review of the most appropriate and expedient endpoints for clinical trials in the relevant subspecialties of medicine. If the FDA were to accomplish a successful streamlining of this process, the rewards both to the public health and to the competitive position of the U.S. pharmaceutical industry would be monumental.

References

1. Drug Master File, Division of Cancer Treatment, National Cancer Institute, on file with the Food and Drug Administration, Rockville, MD.