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CLIENT ADVISORY

FDA ISSUES PROPOSED RULES ON EXPANDED ACCESS AND CHARGING FOR INVESTIGATIONAL DRUGS

DECEMBER 2006

On December 14, FDA issued two linked proposals. The first would clarify and expand the circumstances in which patients not enrolled in clinical trials intended to show the safety and effectiveness of a drug may nevertheless be provided that drug prior to approval, 71 Fed. Reg. 75147 [http://www.fda.gov/OHRMS/DOCKETS/98fr/06-9684.pdf]. This proposal, if adopted, will likely increase pressure on drug companies testing new products for important diseases to make their drugs available to prospective patients prior to receiving approval. The second proposal would clarify and change to an extent the FDA rules on when a company may charge for investigational drugs, 71 Fed. Reg. 75168 [http://www.fda.gov/OHRMS/DOCKETS/98fr/06-9685.pdf]. Charging would continue to be an unrealistic option in most clinical trial settings, but the rules may help facilitate testing of expensive drugs by small companies in some circumstances and also would facilitate comparative trials of marketed products for unapproved uses. Comments are due on each proposal by March 14, 2007.

EXPANDED ACCESS

FDA has always had an informal mechanism for permitting individual patient INDs for particular patients needing access to life-sustaining drugs that have not yet been approved. FDA has in addition had, since 1987, regulations permitting treatment INDs or treatment protocols under existing INDs.

The treatment IND regulation was an FDA response to activism by, among others, AIDs patients seeking access to drugs not yet through the approval system. Recently, FDA has again faced pressure from patient advocates, including a petition from the National Coalition for Cancer Survivorship and the American Society of Clinical Oncology seeking clarification of the rules and a lawsuit by the Abigail Alliance asserting a constitutional right to obtain investigational drugs.

The proposed regulations provide clear guidelines as to when individual access will be permitted. They also continue and modify somewhat the rules

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for treatment protocols and INDs. In addition, the new regulations describe a third category, which FDA terms "Expanded Access for Intermediate-Size Patient Populations."

Several provisions apply to all three expanded access categories: Expanded access is available only for patients to be treated for a serious or an immediately life threatening disease or condition when there is no comparable or satisfactory alternative therapy. In each case, FDA must make a determination that the patient's benefit justifies the potential risks and that those risks are not unreasonable in the context of the disease or condition to be treated. FDA must determine that providing the requested investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the drug.

FDA states that relatively more safety data will be necessary as treatment use is considered for larger potential populations. Thus, FDA says that ordinarily completed Phase 1 safety testing together with preliminary evidence suggesting possible effectiveness—or in some cases where there is no relevant clinical experience, evidence based on preclinical data or a mechanism of action—may be sufficient for individual patient use involving an immediately life-threatening condition not responsive to available therapy. At the other end of the spectrum, a treatment protocol anticipating enrollment of several thousand patients with a serious, but not imminently life-threatening, condition would ordinarily require completion of Phase 3 clinical trials. Such an IND for a condition that is immediately life threatening might be based upon compelling data from Phase 2 trials, or even more preliminary clinical evidence.

For all three types of expanded access, the vehicle remains either an IND or protocol amendment to an existing IND. For a single patient expanded access, the patient's physician would be considered an investigator for purposes of the IND. In each case, the reporting of adverse events, Institutional Review Board (IRB) review, and recordkeeping are required. Expanded access can begin: for a treatment protocol under an existing IND, after IRB approval and submission to FDA; for an individual submission, after FDA authorization; and for an intermediate-size group or for a treatment IND, 30 days after the submission of the IND or on earlier notification by FDA.

Expanded access for an individual patient requires that the patient's physician determine that the probable risk from the drug is not greater than the probable risk from the disease or condition and that FDA determine that the patient cannot obtain the drug under another type of IND. FDA may authorize emergency use by telephone, even prior to receiving a written IND submission.

The new category of expanded access for intermediate-size patient populations may result from an FDA request that a sponsor consolidate a series of individual expanded access applications. FDA contemplates that this type of expanded access may be needed in situations in which a drug

- is not being developed,
- is being developed but the patients in question are unable to participate in the clinical trials, or
- is approved but is no longer available because of safety or other reasons.

Criteria for FDA approval of expanded access for intermediate-size patient populations include enough evidence that the drug is safe at the proposed dose and duration to justify a clinical trial of the drug in the approximate number of patients expected and at least preliminary clinical evidence of effectiveness or of a plausible pharmacological effect.

For treatment INDs or protocols FDA requires either that the drug be currently in investigations in controlled clinical trials or that all clinical trials have been completed and that the sponsor be actively

pursuing approval of the drug for the use at issue. There must be sufficient clinical evidence of safety and effectiveness to support the use, generally from Phase 3 trials but in some cases compelling data from completed Phase 2 trials.

The proposed regulation with respect to treatment INDs would not make significant changes from the current treatment IND regulation. The agency does, however, state that it considers many "open-label safety studies" that are a part of ongoing clinical investigation programs actually to be treatment protocols and states that it will evaluate such open-label studies under the treatment IND criteria. (It does note that continuation phases of clinical trials, in which trial subjects are permitted to continue to receive the test drug, will not be considered treatment INDs.)

The reclassification of an open-label protocol as a treatment protocol may have the effect of increasing publicity concerning the program. FDA notes that sponsors of treatment protocols are required to list the programs on http://www.clinicaltrials.gov. FDA acknowledges that the reclassification may increase enrollment and thus make the trial more expensive for sponsors.

While a significant percentage of the INDs FDA receives are individual patient or emergency INDs, drug companies have not rushed to embrace treatment INDs or treatment protocols. Such submissions make up, FDA says, approximately .2% of all INDs received by the agency each year. All involved understand the reasons why patients with serious or life threatening diseases for which there is no adequate therapy would seek access to unapproved drugs. But the administrative burden and costs associated with making such drugs available, and the potential that programs for treatment during the investigational phase may disrupt development of a drug, make this option unattractive for most in the pharmaceutical industry. This is true, in most cases, even though there may be an opportunity for some cost recovery under current regulations, and also under the proposed new regulations discussed below.

CHARGING FOR INVESTIGATIONAL DRUGS

In proposing to change its rules for charging for drugs involved in clinical investigation programs, FDA noted that one significant area of requests to charge for drugs was not anticipated by current regulations, i.e., situations in which clinical trials involved drugs other than those of the sponsor. In those cases, in which the sponsor was required to purchase the drug from other manufacturers for use in control groups or in combination therapy, sponsors had asked for permission to charge for those drugs. The proposed revised rule will permit companies to charge for such drugs. This permission will be particularly useful in situations in which the sponsor of the clinical trial is not the developer of any of the drugs being tested. This could occur, for example, when an institution or third-party provider investigates potential off-label uses of marketed drugs. Even in such trials, however, the sponsor will have the burden of convincing FDA that the clinical trial is of adequate design to evaluate the safety or effectiveness of a new indication or to provide important safety information relating to an approved indication.

The proposed regulation also seeks to facilitate charging for drugs provided in individual or intermediate size expanded access programs. To avoid having such charging be a substitute for obtaining approval, the sponsors would be required to provide evidence of sufficient enrollment in any ongoing clinical trials and of progress in developing the drug for marketing approval.

Under the proposed regulation, as with the existing one, FDA could permit a sponsor to charge for its own drug in a clinical trial in limited circumstances. To qualify, the sponsor would be required to show that charging is necessary to facilitate development of a promising new drug or an indication that might not otherwise be developed or to obtain important safety information that

might otherwise not be obtained. In addition, the sponsor must convince FDA that the trial in question will provide evidence of potential clinical benefit that would represent a significant advantage over other available therapies. FDA will, in any case, approve charging only when the cost of the drug is extraordinary.

The costs recoverable under the regulation are limited to the direct costs of making the drug available. Direct costs include cost per unit to manufacture the drug or cost to acquire it from another manufacturing source and cost to ship and handle the drug. Charging cannot include costs attributable to expenditures for physical plant and equipment that were incurred for eventual manufacture for commercial sale after approval, nor do they include research and development, administrative, labor, or any other costs that would be incurred even if the clinical trial did not go forward.

The proposal would permit recovery of the cost of administering treatment use programs for intermediate size patient populations and for treatment INDs and protocols. Such costs associated with expanded access for individual patients cannot be recovered, on the theory that those costs would be minor. Administrative costs such as monitoring an expanded use program, complying with IND reporting requirements, and other administrative responsibilities may be included in the permitted charge. In each case, the sponsor must provide supporting documentation and in some cases may be required to provide independent certification of its costs.

One substantive change from the existing regulation would require FDA permission to charge in all circumstances. Currently, authorization to charge for an investigational drug in a treatment protocol or treatment IND goes into effect automatically 30 days after receipt of a request by FDA unless FDA notifies the sponsor otherwise.

As FDA notes, charging patients for an investigational drug is unusual. Generally, the cost of the test drug and any controls is considered an appropriate cost of drug development. The proposed rules are very unlikely to change that pattern. A significant proportion of patients who pay for pharmaceuticals obtain reimbursement either from the government or through third-party payers. Obtaining reimbursement for an investigational drug is likely to be difficult in most cases, so that charging for the drug would seriously complicate patient recruitment. Moreover, and significantly, the decision to charge for a drug in an investigational trial creates an awkward situation at the point of launch after approval. Because the cost during the trial would not include the cost of research nor the return on investment that is necessary for a high risk industry, the amount charged during the trial would necessarily be much lower than the amount for which the sponsor would seek to market the product after approval. Explaining that difference in cost to patients, to patient advocacy groups, and to government and other third-party payers would often be a challenge.

If you would like additional information about these proposals or would like to discuss them, please contact:

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