Slouching Toward a Cure?: Court, FDA Ponder Expanded Patient Access to Investigational Drugs, Raising Constitutional & Commercial Issues

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On December 11, 2006, the FDA proposed two rules designed to expand early access by patients to investigational drugs during clinical development phases, and to further facilitate sponsors' ability to charge for both investigational and approved drugs used in clinical trials. And, in March 2007, a federal appeals court heard re-argument in Abigail Alliance v. von Eschenbach, a case that could establish a much broader legal right for patients to gain access to unapproved investigational drugs. The FDA proposals, if finalized, and the Abigail Alliance case, have the potential to benefit both patients and pharmaceutical companies, and particularly Specialty Pharma companies whose only products are still in the investigational phase, but also pose difficult challenges to FDA's ability to thoroughly review the safety and efficacy of new drugs prior to their widespread use in patients.

BACKGROUND

Under the Federal Food, Drug, and Cosmetic Act (FDCA), "new drugs" may not be commercially marketed before receiving FDA approval, and even then, they may not be promoted for uses beyond those specifically approved by the FDA. During clinical trials on new drugs, however, some patients are given the test drug, while others in the study receive a placebo or some other approved active-control drug. For serious or life-threatening diseases, there is often no adequate approved drug treatment available, and thus use of an experimental drug sometimes offers the only hope for improvement or even survival. But given the length of the investigational and FDA review processes, drugs that show promise for serious diseases often are not available to dying patients for many years after the potential benefit has been identified. This has long created pressure on the FDA and pharmaceutical companies to make promising experimental drugs available to patients other than those enrolled in clinical trials for the drug, and more recently has generated constitutional litigation challenging the fundamental principle of the Federal Food, Drug, and Cosmetic Act that drugs must receive FDA approval prior to being made available to patients outside of regulated clinical trials.

A related issue under consideration by FDA is whether, and to what extent, drug companies should be allowed to charge patients for the drugs they receive in clinical trials. Drug companies may not commercialize unapproved drugs, meaning that in most cases, they may not charge for drugs in clinical development. Given the tremendous expense of drug development, the ability to recoup some of the costs incurred during drug testing is of particular interest to early stage and Specialty Pharma companies, as well as academic research institutions, which may be operating on small budgets and uncertain future financing.

Inadequacy of Current Access & Charging Policies

The FDA has long recognized the forgoing concerns and has had policies and regulations that, in a limited way, allowed early access to investigational drugs, and in some circumstances, permitted sponsors to charge for investigational drugs. However, the FDA believes that the existing policies have limitations that now need modernization. In announcing the proposed rules, the FDA stated that "the existing regulations did not adequately describe the full range of [expanded access] programs available," and noted concern that "the lack of specific criteria and submission requirements results in disparate access to treatment use for different types of patients and diseases." With respect to charging for investigational drugs, the FDA has found that few requests have been made to charge for investigational drugs, but that more commonly, sponsors request permission to charge for approved drugs used as comparators in clinical trials, or used in third-party studies seeking new indications of approved drugs. Moreover, the agency believes that "the current charging rule is not very specific and does not provide sufficient guidance to sponsors on the costs that

can be recovered" in clinical trials.

In response to FDA's earlier refusal to grant its petition seeking the adoption of a broad early access policy, the Abigail Alliance sued FDA challenging the constitutionality of FDA's general refusal to allow dying patients to obtain and use investigational drugs that have successfully completed Phase I clinical studies and have been shown to be sufficiently safe to be further tested in larger Phase II studies. In 2006, the U.S. Court of Appeals for the D.C. Circuit issued a controversial 2-1 decision holding "that where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials, warrants protection under the Due Process Clause." That decision was later vacated and the case was re-argued en banc before ten judges of the D.C. Circuit on March 1, 2007. A ruling is expected later this year.

THE PROPOSED RULES

Expanded Treatment Access

The expanded access proposed rule seeks to make it easier for patients with serious or life-threatening diseases or conditions to gain access to experimental drugs. It does so in part by proposing explicit criteria for access by individual patients and by intermediate-size patient populations, in addition to the larger-size patient populations for which treatment INDs have historically been available. The baseline criteria for allowing treatment access to investigational drugs in all scenarios are: 1) that the drug is intended to treat a "serious or immediately life-threatening disease or condition" for which there is "no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;" 2) that the potential patient benefit outweighs the potential risks; and 3) that providing the drug for treatment uses will not interfere with the clinical investigations that could support marketing approval. Although the first criterion is essentially unchanged from current regulations, in proposing to codify the second and third criteria, the FDA hopes to clarify and expand the circumstances that can support treatment use of investigational drugs.

Of particular interest, the FDA recognizes that "the evidence needed to demonstrate the safety and potential benefit of a proposed use varies with the size of the population to be treated and the relative seriousness of the disease or condition to be treated." Thus, the proposed rule would create a sliding scale for the required levels of evidence of safety and potential benefit needed to allow early access, depending on the seriousness of the disease and the size of the proposed patient treatment population. With respect to the safety/benefit/seriousness evaluation, the FDA explains that "as the seriousness of the disease increases, it may be appropriate to authorize expanded access use based on less data, still taking the size of the patient population into account."

At one end of the spectrum, to support expanded access for large patient populations, the FDA would generally require safety and effectiveness data from Phase III clinical trials, or in cases of immediately life-threatening diseases, compelling data from Phase II trials. At the other end of the spectrum, for single-patient access requests, where the patient has an immediately life-threatening disease and has not responded to available therapy, "the evidentiary burden could be very low" and early access may be allowed based on Phase I safety data (using doses similar to those to be used in the patient) and some appropriate data to suggest potential effectiveness. And, when a patient's condition is immediately life-threatening, the FDA may allow access based only on preclinical data and/or evidence as to the mechanism of action of the drug.

The safety/potential benefit considerations with respect to intermediate-size patient populations are, unsurprisingly, somewhere between those to be applied for single-patient access and large-scale treatment INDs. As the FDA explains, the criteria for intermediate-size populations, "there must be at least some preliminary clinical evidence of effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population."

The proposal's approach to intermediate-size patient populations is perhaps the most potentially useful aspect of the proposed rule because it may fill a gap in current practice between large-scale treatment INDs and single-patient compassionate-use exceptions. The FDA contemplates that this approach may be used in several circumstances not adequately addressed under current policy.

Specifically, intermediate-size population expanded access may be possible for drugs that are not being developed because, for example, the disease or condition is too rare to enable the sponsor to adequately recruit patients for clinical trials. In

addition, such access programs may be approved where the drug is being actively developed, but patients requesting the drug are unable, or ineligible, to participate in the clinical trials. Similarly, expanded access may be granted for approved drugs that are no longer being marketed, due to safety reasons or because of unresolved non-compliance with current Good Manufacturing Practices requirements (as long as the safety or manufacturing issues do not pose a risk that is unreasonable in comparison to the risks of the disease being treated).

Charging for Drugs in Clinical Trials

Like the expanded access proposed rule, the FDA's proposed rule for charging for drugs in clinical trials does not present an entirely new concept as the FDA's policy has previously provided for potential charging in limited circumstances. However, the FDA has identified aspects of its policy that require clarification and limited expansion, as proposed in the new rule and described further on. The charging rule would clarify the circumstances in which patients can be charged for drugs (both experimental and approved) used in clinical trials. The rule would permit charging for the sponsor's own drug if the drug, a new indication for the drug, or new safety data might not otherwise be developed, the trial is essential to the development of a new drug or would support a significant labeling change for an approved drug, and the charging is necessary to conduct the trial. Sponsors would also be able to charge for use of another company's approved drug when co-administered with, or used as a comparator to, an investigational drug, or in trials evaluating a new use for an approved drug.

As a baseline matter, however, the FDA makes clear that charging for investigational drugs will not become the norm, explaining that "[g]enerally, the costs of conducting a clinical trial are costs that the sponsor should bear. Conducting a clinical trial is part of the drug development process, and drug development is an ordinary business expense for a commercial sponsor. If the investigational drug proves successful in clinical trials, the sponsor will recoup its development costs by marketing the drug for its approved indication." Moreover, as the FDA notes, clinical trial subjects put themselves at risk, in part for the benefit of the sponsor, and in most cases, subjects are compensated by the sponsor for their participation, rather than being charged for the drugs used in the study.

Importantly, the FDA cautions that sponsors have sometimes interpreted existing regulations too broadly in the past. For example, sponsors have sought charges intended to cover multiple types of costs associated with the research, development, and handling of the drug, or even costs of facilities used to commercially manufacture the drug. Thus, the agency makes clear that the intent of its current and proposed charging policies is not to allow recovery of the costs of research and development of a drug before marketing.

Specifically, the FDA states that the "purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of a drug when the drug is extraordinarily expensive. Thus, [the proposal] would limit cost recovery to the direct costs of making the investigational drug available in these situations. Indirect costs could not be recovered."

Direct costs that may be recoverable would include, on a per-unit basis, costs of manufacturing (materials, labor, non-reusable supplies), and costs to acquire the drug from another source, including direct shipping, handling, and storage costs. Non-recoverable indirect costs include physical plant and equipment intended for commercial-scale manufacturing, and research, development, administrative, labor, and other costs that would be incurred even without the clinical trials under which cost recovery is sought.

One circumstance in which the FDA has always recognized a legitimate basis for charging for investigational drugs is in the treatment IND context, because the use of a drug in this context does not benefit the sponsor by generating significant useful safety and efficacy data to support FDA approval. Rather, these programs are designed to treat patients, just as in the post-approval commercial context. Thus, the agency proposes to retain its current regulations, in expanded form, to facilitate charging in the newly defined expanded access categories (single-patient access, and intermediate-size patient populations). Recoverable costs for expanded access treatment uses would also include the costs of administering the drug in such programs, monitoring the expanded access use, complying with IND reporting requirements, and other administrative costs incurred in an expanded access program.

Finally, when an approved drug is being studied by an

entity other than the sponsor/manufacturer — such as active-drug controls in a trial of a sponsor's investigational drug, or in third-party trials studying a new indication for the approved drug — the FDA intends to set a lower threshold for allowing charging for the approved drug. This approach may prove especially beneficial to academic institutions, or smaller independent research organizations.

IMPLICATIONS

The Constitutional reasoning of the D.C. Circuit's original decision in Abigail Alliance sent shock waves through FDA, the pharmaceutical industry, and patient advocacy groups. Although Abigail Alliance is itself a patient advocacy group, several other patient groups sided with FDA in opposition to the original appeals court's decision, arguing among other things, that the type of expanded access endorsed by the court would lead to fewer patients enrolling in the pivotal clinical trials necessary to definitively establish whether a new treatment does in fact work, and thus could cause a long-term reduction in treatment options for the seriously ill and dying.

Pharmaceutical companies may be concerned about product liability implications, charging limitations, and the possibility that any broad early access rule could lead FDA to require even more data at the earliest stages of drug development, further escalating the cost and time required to bring new drugs to market. Regardless of the outcome of the court's re-review, it is expected that the losing side will seek a final ruling from the Supreme Court.

Although the concerns raised in opposition to the Abigail Alliance case have also been raised by some in the context of FDA's proposed rules, Specialty Pharma companies should carefully evaluate their clinical programs in the context of the FDA's proposed rules, as there may be unrealized opportunities for wider distribution and cost recovery during the critical clinical evaluation period. For some companies in tight financial circumstances, even the relatively incremental benefits of the expanded access and charging proposals could make a material difference in a company's ability to reach the finish line of FDA approval without additional venture (or other) funding, or further dilution of ownership/control of the company. ◆

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Mr. James Czaban is a Partner in the Washington, DC, office of Wilmer Cutler Pickering Hale & Dorr LLP (WilmerHale), where he leads the firm's FDA Department. In addition to his nearly 15 years of private practice in Food & Drug law, Mr. Czaban has lectured widely on topics of FDA regulation of pharmaceuticals, including at Harvard University, Fordham Law School, Seton Hall Law School, Hastings College of Law, the American Bar Association, the Food & Drug Law Institute (FDLI), the Biotechnology Industry Organization (BIO), the Regulatory Affairs Professionals Society (RAPS), the Drug Information Association (DIA), and numerous other pharmaceutical industry symposia. He is the author of chapters in three legal treatises on Food & Drug law, writes regular legal columns for various trade publications, and is a member of the Editorial Advisory Boards of *Specialty Pharma* and *Drug Delivery Technology* magazines. He was recognized as a "Top Lawyer" in Food & Drug Law by *Washingtonian Magazine*. Sponsors who have questions about the proposed rules, the *Abigail Alliance* case, or other pharmaceutical regulatory issues can contact Jim at (202) 663-6292, or james.czaban@wilmerhale.com.