Proposed Rules Regarding Requirements for Expanded Access to Investigational Drugs and Charging for Investigational Drugs

On December 14, 2006, the Food and Drug Administration (FDA) published in the Federal Register two proposed rules that would amend FDA’s regulations governing expanded access to investigational drugs for treatment use and charging for investigational drugs. Comments on these proposals must be submitted by March 14, 2007.

In the first proposed rule, FDA proposes to clarify existing regulations pertaining to access, outside of clinical trials, to investigational drugs intended for the treatment of serious or immediately life-threatening diseases or conditions. FDA would continue to permit expanded access for large groups of patients under a treatment IND or protocol and expedited access for individual patients in emergency situations. The most significant changes FDA is proposing would specify criteria for access to investigational drugs by individual patients and create a new category of expanded access for small groups of patients.

In the second proposed rule, FDA proposes to clarify the existing regulation on charging for investigational drugs, expand the circumstances in which charging for an investigational drug may be permitted, and describe the costs sponsors may recover from patients for use of an investigational drug. The most significant changes FDA is proposing would allow sponsors of clinical trials to charge patients for approved drugs obtained from other sources and provide criteria for charging for drugs provided as part of an expanded access program.

Part I of this memorandum summarizes current statutory and regulatory requirements for expanded access to investigational drugs and charging for investigational drugs. Part II describes recent developments relating to expanded access. Part III summarizes the proposed changes to the current regulations governing expanded access to investigational drugs and charging for investigational drugs.

I. Summary of Current Statutory and Regulatory Requirements

A. Expanded Access to Investigational Drugs

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) states that “[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of a new drug application (NDA) or abbreviated new drug application (ANDA) is effective with respect to that drug.” Before a drug is eligible for approval, there must be a finding of “substantial evidence that the drug will have the effect it purports or is represented to have.” To gather data

2 Id. at 75168 (to be codified at 21 C.F.R. part 312).
4 Id. § 355(d)(5).
needed for approval, however, a sponsor must be able to ship the drug for testing. Accordingly, section 505(i) of the FDCA creates an exemption that allows manufacturers to distribute unapproved new drugs to complete the clinical trials necessary to support an NDA.\(^5\)

Pursuant to its statutory authority to issue regulations for exempting investigational drugs from the NDA requirement,\(^6\) FDA published regulations in part 312 that specify the content of investigational new drug applications (INDs). These regulations also describe the three phases of clinical testing typically performed to generate the evidence of safety and effectiveness required for approval. Phase 1 includes the initial introduction of an investigational new drug into humans and is generally conducted in a limited number of healthy volunteer subjects or, in some instances, ill patients to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence of effectiveness.\(^7\) It is not until Phase 2 that controlled clinical studies are conducted to obtain preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition.\(^8\) Phase 2 testing also helps determine the common short-term side effects and risks associated with the drug and usually includes several hundred people.\(^9\) Phase 3 studies, which involve several hundred to several thousand people, gather the additional safety and effectiveness information necessary to evaluate the overall benefit-risk relationship of the drug and provide the basis for extrapolating the results to the general population and transmitting that information in the physician labeling.\(^10\)

The IND regulations date to 1938\(^11\) and were substantially revised in 1963\(^12\) and again in 1987.\(^13\) For many years prior to 1983, FDA permitted treatment use of investigational drugs – i.e., use primarily to treat a patient rather than to answer safety or effectiveness questions about the drug – on an informal basis.\(^14\) Prior to 1987, however, the regulations did not formally recognize this practice. In 1987, citing its authority under section 505(i),\(^15\) FDA finalized regulations formally recognizing its practice of permitting additional exemptions on a compassionate basis for treatment of patients with investigational drugs outside the scope of ordinary clinical trials.\(^16\)

These regulations, which FDA is now proposing to amend, recognize only one type of expanded access program, the “treatment IND” or “treatment protocol.”\(^17\) FDA will permit an

\(^{5}\) Id. § 355(i).
\(^{6}\) Id. § 355(i)(1).
\(^{7}\) 21 C.F.R. § 312.21(a).
\(^{8}\) Id. § 312.21(b).
\(^{9}\) Id.
\(^{10}\) Id. § 312.21(c).
\(^{13}\) 52 Fed. Reg. 8798 (March 19, 1987).
\(^{16}\) 21 C.F.R. §§ 312.34-312.36.
\(^{17}\) Id. §§ 312.34, 312.35. A treatment IND is a new IND submitted to FDA by a sponsor or a physician for treatment use of an investigational drug. A treatment protocol is an amendment to an existing IND submitted by a sponsor for treatment use of an investigational drug.
investigational drug to be used for treatment, under a treatment IND or treatment protocol, if: (1) it is intended to treat a serious or immediately life-threatening disease; (2) no comparable or satisfactory alternative therapy is available for treatment; (3) the drug is under investigation in a controlled clinical trial under an IND or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence. For a serious disease, FDA may allow access during Phase 3 trials or, in appropriate circumstances, during Phase 2 trials. For an immediately life-threatening disease, FDA may permit access earlier than Phase 3, but "ordinarily" not earlier than Phase 2.

The regulations also implicitly recognize the availability of investigational drugs to individuals outside of clinical trials, with the inclusion of an expedited procedure for emergency situations. The regulation in question does not, however, state the criteria that govern FDA's decision in this situation. Moreover, the 1987 regulations did not provide a procedure, or criteria, that would apply if an individual sought access to an investigational drug in a non-emergency situation.

Due in part to this lack of regulatory guidance for individuals seeking treatment use and to the desire to ensure the availability of treatment use programs for individuals facing serious and life-threatening diseases, Congress amended the FDCA in 1997 to provide statutory authorization for expanded access use. The new statutory provision – section 561 of the FDCA – largely parallels FDA's regulations describing procedures for large groups of patients to access investigational drugs under a treatment IND or protocol and authorizing expedited use of investigational drugs in emergency situations. But, unlike FDA's regulations, it explicitly permits an individual patient, acting through a physician, to obtain access to an investigational therapy if the following conditions are met: (1) a licensed physician makes a determination that the patient has no comparable or satisfactory alternative therapy available to treat the condition, and that the probable risk to the patient from the treatment is not greater than the probable risk from the condition; (2) FDA makes an affirmative determination that there is "sufficient evidence of safety and effectiveness" to support the use of the product in the patient's case; (3) FDA makes an affirmative determination that providing the product to the patient will not interfere with the initiation, conduct, or completion of clinical trials to support marketing approval; and (4) a protocol has been submitted to FDA in accordance with section 505(i) of the FDCA. FDA did not propose new regulations until this year.
B. Charging for Investigational Drugs

FDA’s current regulations generally prohibit sponsors from charging for the use of investigational drugs.\(^{26}\) Testing is considered part of the normal cost of doing business.\(^{27}\) There are two exceptions to this prohibition. First, a sponsor may charge patients for use of its investigational drug in a clinical trial if the sponsor receives prior FDA approval.\(^{28}\) The sponsor must provide FDA with a written explanation stating the reason charging is necessary.\(^{29}\) Second, a sponsor may charge patients for use of an investigational drug under a treatment IND or protocol if: (1) there is adequate enrollment in the ongoing clinical investigations under the IND; (2) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (3) the drug is not being commercially promoted or advertised; and (4) the sponsor is actively pursuing marketing approval with due diligence.\(^{30}\) The sponsor must notify FDA in writing in an information amendment to its IND before it may begin charging for an investigational drug for treatment use.\(^{31}\) Authorization to charge takes effect automatically 30 days after FDA receives the information amendment unless the agency notifies the sponsor otherwise.\(^{32}\) Whether the sponsor charges in a clinical trial or for treatment use, FDA regulations prohibit charging more than is necessary to recover the costs of manufacture, research, development, and handling of the investigational drug.\(^{33}\)

II. Recent Developments

FDA’s proposal to revise its regulations governing expanded access to investigational drugs and charging for investigational drugs comes at a time when patient advocacy groups and their allies have been pressuring the agency to modify those regulations and related agency policies. Criticisms aimed at the current regulations range from calls for greater clarity to claims of unconstitutionality. Some critics contend that FDA has failed to provide specific criteria for obtaining expanded access, thus resulting in disparate access to investigational drugs and lack of widespread knowledge of these programs.\(^{34}\) Others have argued that FDA’s policy restricting access to investigational drugs showing initial evidence of safety and effectiveness violates a fundamental right of terminally ill patients.\(^{35}\) Some critics claim that barring the commercial sale of investigational drugs deters drug manufacturers from making their products available for treatment use,\(^{36}\) while others have stated that drugs companies should not charge at all for use of their investigational drugs for

\(^{26}\) 21 C.F.R. § 312.7(d).
\(^{27}\) Id.
\(^{28}\) Id. § 312.7(d)(1).
\(^{29}\) Id.
\(^{30}\) Id. § 312.7(d)(2).
\(^{31}\) Id. The information amendment must be submitted in accordance with 21 C.F.R. § 312.31. Id.
\(^{32}\) Id.
\(^{33}\) Id. § 312.7(d)(3).
\(^{36}\) Id. at ¶ 15.
treatment use. These concerns have formed the basis for citizen petitions, litigation against the agency, and even proposed federal legislation.

On June 11, 2003, the Abigail Alliance and Washington Legal Foundation (WLF) submitted a citizen petition to FDA requesting that the agency amend its part 312 regulations to establish a mechanism called “Tier 1 Initial Approval.”38 Drugs with initial approval could be made available for commercial sale to patients with life-threatening diseases, who have no alternative government approved treatment options.39 Drugs eligible for initial approval would consist of those for which Phase 1 data established a safety profile sufficient to support conduct of Phase 2 or Phase 3 trials and for which case history data from a small number of patients provide initial evidence of effectiveness.40

After FDA failed to respond to their citizen petition,41 the Abigail Alliance and WLF filed a lawsuit against the agency on July 28, 2003, claiming FDA’s policy of prohibiting the sale of post-Phase 1 investigational drugs showing initial evidence of safety and effectiveness to terminally ill patients not in Phase 2 clinical trials is unconstitutional.42 The United States District Court for the District of Columbia dismissed the case in August 2004 for failure to state a claim.43 On May 2, 2006, a divided panel of the United States Court of Appeals for the District of Columbia reversed the lower court’s decision, finding that mentally competent, terminally ill patients with no government-approved treatment option have a constitutional right to access potentially life-saving investigational drugs that FDA has determined, after Phase 1 trials, are sufficiently safe for expanded human trials.44 The district court had not reached the question whether the challenged FDA policy violated this protected liberty interest, so the panel remanded the suit to the district court “to determine whether the FDA’s policy barring access to post-Phase I investigational new drugs by terminally ill patients is narrowly tailored to serve a compelling governmental interest.”45 FDA responded by petitioning the D.C. Circuit for an en banc rehearing.46 The court granted this request in November 200647 and will hear oral arguments on March 1, 2007.48

39 Id. at 5-6.
40 Id. at 5.
45 Id.
The National Coalition for Cancer Survivorship (NCCS) and the American Society of Clinical Oncology (ASCO) filed a separate citizen petition with FDA on March 27, 2006, requesting that the agency issue guidance describing procedures and standards for initiating expanded access programs for investigational drugs.\textsuperscript{49} Emphasizing that expanded access programs should not impede ongoing trials or delay marketing approval, the petition recommended a systematic approach for expanded access.\textsuperscript{50} In particular, it noted that expanded access for individual patients places substantial burdens on sponsors and physicians and thus recommended the use of standard protocols and model consent forms.\textsuperscript{51} The petition also described variables that FDA should take into consideration when evaluating clinical trial data to allow expanded access – such as the nature and strength of the evidence, unmet patient need, likelihood and imminence of marketing approval, and drug availability.\textsuperscript{52} It further stated that FDA should urge sponsors to provide drugs free of charge to patients in expanded access programs.\textsuperscript{53} FDA has not yet responded to the petition.

In addition, legislation was introduced during the 109th Congress to create a new approval process for access to investigational drugs for treatment use.\textsuperscript{54} Like the petition submitted by the Abigail Alliance and WLF, the proposed legislation created a “Tier 1 Approval” process allowing access to investigational drugs for seriously ill patients who have exhausted all other treatment options.\textsuperscript{55} To apply for this approval, a sponsor would submit an application to FDA with data from a completed Phase 1 trial, preliminary evidence of effectiveness based on information such as data from case histories, and assurance that the sponsor would continue clinical investigations to obtain Tier III Approval.\textsuperscript{56} FDA could either approve the application or submit it to an Accelerated Approval Advisory Committee for review.\textsuperscript{57} As a condition to obtaining access to the drug, patients would provide written informed consent, waive the right to sue the manufacturer or sponsor of the drug and the physicians who prescribe it, and permit the use of data and information about the patient’s use of the product by the manufacturer to support approval of the product.\textsuperscript{58} The 109th Congress ended without any action taken on the legislation.

\textsuperscript{47} Abigail Alliance v. von Eschenbach, No. 04-5350 (Nov. 21, 2006).
\textsuperscript{48} Abigail Alliance v. von Eschenbach, No. 04-5350 (Nov. 22, 2006).
\textsuperscript{50} Id. at 2, 4.
\textsuperscript{51} Id. at 3.
\textsuperscript{52} Id. at 5.
\textsuperscript{53} Id. at 7.
\textsuperscript{54} Access, Compassion, Care, and Ethics for Seriously Ill Patients Act (ACCESS Act), S. 1956 and H.R. 6303, 109th Cong.
\textsuperscript{55} Id. § 3(b).
\textsuperscript{56} Id. § 3(b)(1). Tier II approval would be roughly the same as fast track approval under current law.
\textsuperscript{57} Id. § 3(b)(2).
\textsuperscript{58} Id. § 3(b)(5)(B).
III. Summary of the Proposed Rules

A. Expanded Access to Investigational Drugs

FDA’s proposed regulations would permit expanded access for individual patients, intermediate-size patient populations, and larger patient populations.

1. Requirements for All Expanded Access Uses

In each type of expanded access, FDA would have to determine that: (1) the patient or patients seeking treatment use have a serious\(^{59}\) or immediately life-threatening\(^{60}\) disease or a condition with no comparable or satisfactory alternative therapy\(^{61}\); (2) the potential patient benefit justifies the potential treatment use risks and those risks are not unreasonable in the context of the disease or condition to be treated; and (3) providing the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use.\(^{62}\) Additional criteria would apply, depending on the type of expanded access at issue.

The amount of evidence FDA would require to satisfy the second criterion would depend on the type of expanded access (due to differences in the number of patients in each category) and on the seriousness of the disease.\(^{63}\) In general, the agency would require more evidence of safety and effectiveness for treatment of a larger population of patients than for treatment of a smaller number of patients.\(^{64}\) Fewer data would be required for more serious diseases.\(^{65}\) For instance, completed Phase 1 safety testing of an investigational drug, along with preliminary evidence suggesting possible effectiveness, would generally be sufficient to support treatment use by an individual patient with an immediately life-threatening disease.\(^{66}\) In some situations, access might be based on preclinical data or on the mechanism of action.\(^{67}\) This proposed standard for access to treatment use appears to be similar to that proposed by the Abigail Alliance and the WLF in their petition to FDA, which requested access to experimental drugs prior to Phase 2 testing.\(^{68}\) In contrast, FDA would ordinarily require data from Phase 3 trials for treatment of a broad population of patients.

---

\(^{59}\) Although the proposed rule does not define a “serious disease or condition,” it notes that FDA has described it elsewhere as referring to conditions that have an “important effort on functioning (e.g., stroke, schizophrenia, rheumatoid arthritis, osteoarthritis) or on other aspects of quality of life (e.g., chronic depression, seizures).” 71 Fed. Reg. 75147, 75151 (Dec. 14, 2006).

\(^{60}\) The proposed rule defines an “immediately life-threatening disease” as “a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.” Id. at 75166; proposed 21 C.F.R. § 312.300(b).

\(^{61}\) In some cases, available therapy might mean a treatment that is not regulated by FDA (e.g., surgery) or an off-label use supported by compelling literature evidence.” Id. at 75151.

\(^{62}\) Id. at 75166; proposed 21 C.F.R. § 312.305(a).

\(^{63}\) Id. at 75151.

\(^{64}\) Id.

\(^{65}\) Id.

\(^{66}\) Id.

\(^{67}\) Id.

\(^{68}\) See Abigail Alliance & Washington Legal Found., Citizen Pet. to FDA, In re Tier 1 Approval Program to Expedite the Availability of Lifesaving Drugs, 2-3 (June 11, 2003).
with a serious illness or compelling data from Phase 2 trials for larger patient groups with immediately life-threatening diseases.69

The proposed rule, like the current regulation, would require a new IND or a protocol amendment to an existing IND before patients could obtain expanded access to an investigational drug.70 Proposed section 312.305(b)(2) describes the contents of an expanded access submission.71 Treatment use under a protocol amendment to an existing IND for individual patients and intermediate-size patient groups could begin after IRB approval and submission of the amendment to FDA.72 Treatment use of an investigational drug under a new IND submitted for any of the three types of expanded access or under a treatment protocol for large patient populations could begin 30 days after FDA received the IND (or upon earlier notification by FDA).73

2. Additional Requirements for Expanded Access for Individual Patients

For an individual patient to qualify for expanded access, a physician would also be required to determine that the probable risk to the patient from the drug is not greater than the probable risk from the disease or condition, and FDA would need to conclude that the patient could not obtain the drug under another type of IND (such as through participation in a clinical trial).74 Either the sponsor or the patient’s physician could request the expanded access in question, if the investigational drug were the subject of an effective IND.75 Treatment use would be limited to a single course of therapy for a specific time period unless FDA authorized otherwise.76 As is the case under current regulations, if an emergency were to require treatment of an individual with an investigational drug before a written submission could be made, FDA could authorize expanded access use by telephone.77 The sponsor or physician requesting emergency use would have to provide a written submission within five working days of FDA’s authorization.78

3. Additional Requirements for Expanded Access for Intermediate-Size Patient Populations

FDA is also proposing a regulation to govern expanded access for intermediate-size patient populations.79 FDA would generally ask a sponsor to proceed under this new regulation once

---

70 Id. at 75166; proposed 21 C.F.R. § 312.305(b)(1).
71 Id.
72 Id.; proposed 21 C.F.R. § 312.305(d)(2).
73 Id. at 75167; proposed 21 C.F.R. § 312.305(d)(1), (d)(2)(ii).
74 Id.; proposed 21 C.F.R. § 312.310(a).
75 Id.; proposed 21 C.F.R. § 312.310(b)(1). The sponsor would submit a protocol to its IND. The physician would submit a new IND, referring (with consent) to the existing IND and providing any other information required. Id.; proposed 21 C.F.R. § 312.310(b)(2)-(3).
76 Id.; proposed 21 C.F.R. § 312.310(c).
77 Id.; proposed 21 C.F.R. § 312.310(d).
78 Id.; proposed 21 C.F.R. § 312.310(d)(2).
79 Id.; proposed 21 C.F.R. § 312.315.
the agency received 10 requests for expanded access for individual patients.\textsuperscript{80} The agency suggests that expanded access for intermediate-size patient populations would be needed when a promising drug is not being developed (possibly due to a lack of study subjects with a particular rare disease); when patients requesting expanded access to the drug are unable to participate in the clinical trials; or when a drug is approved but is no longer marketed for safety or other reasons.\textsuperscript{81}

In addition to the general criteria that would apply in all expanded access situations, FDA proposes two additional criteria that would have to be met for expanded access for intermediate-size patient populations. Specifically, FDA would need: (1) to conclude that there is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial in the approximate number of patients expected to receive the drug, and (2) to determine that there is at least preliminary clinical evidence of effectiveness of the drug or a plausible pharmacologic effect of the drug.\textsuperscript{82}

To submit a request for expanded access for intermediate-size patient populations, a sponsor would have to state whether the drug is being developed and describe the patient population to be treated.\textsuperscript{83} If the drug is not being developed, the sponsor would have to explain why it cannot be developed for the expanded access use and under what circumstances it could be developed.\textsuperscript{84} If the drug is being investigated in a clinical trial, the sponsor would have to state why the patients seeking expanded access cannot be enrolled in the trial and under what circumstances they could be.\textsuperscript{85} After expanded access is authorized, FDA would determine based upon its review of the sponsor’s annual IND report whether the treatment use could be reauthorized.\textsuperscript{86} If the number of patients enrolled increased – typically to over 100 individuals\textsuperscript{87} – FDA could ask the sponsor to submit instead a treatment IND or protocol.\textsuperscript{88} The sponsor would be required to ensure that physicians comply with the protocol and regulations applicable to investigators.\textsuperscript{89}

4. Additional Requirements for Expanded Access Under a Treatment IND or Protocol

A treatment IND or protocol would enable widespread treatment use of an investigational drug. As is true under current regulations, FDA would permit a treatment IND or protocol only if the drug is under investigation in a controlled clinical trial or all clinical trials have been completed, and only if the sponsor is actively seeking with due diligence marketing approval for the

\textsuperscript{80} Id. at 75154, 75167; proposed 21 C.F.R. § 312.315.
\textsuperscript{81} Id. at 75167; proposed 21 C.F.R. § 312.315(a).
\textsuperscript{82} Id.; proposed 21 C.F.R. § 312.315(b).
\textsuperscript{83} Id. at 75168; proposed 21 C.F.R. § 312.315(c)(1).
\textsuperscript{84} Id.; proposed 21 C.F.R. § 312.315(c)(2).
\textsuperscript{85} Id. proposed 21 C.F.R. § 312.315(c)(3).
\textsuperscript{86} Id. proposed 21 C.F.R. § 312.315(d)(1).
\textsuperscript{87} See id. at 75154.
\textsuperscript{88} Id. at 71568; proposed 21 C.F.R. § 312.315(d)(1)(iii).
\textsuperscript{89} Id.; proposed 21 C.F.R. § 312.315(d)(2).
expanded use.\textsuperscript{90} In addition, the sponsor would be required to ensure that physicians comply with the protocol and regulations applicable to investigators.\textsuperscript{91}

In an attempt to address its concern that studies frequently described as “open-label safety studies” have been used to make investigational drugs available to large patient populations for treatment use, FDA states in the preamble to the proposed rule that it will evaluate whether proposals for open-label safety studies should be reclassified as treatment INDs or protocols.\textsuperscript{92} According to FDA, a proposal providing broad access to a drug in the later stages of development, which lacks systemic data collection and an appropriate design for safety evaluation, would likely be subject to reclassification.\textsuperscript{93} FDA emphasizes, however, that the continuation phase of a clinical trial could not be reclassified as treatment IND or protocol because enrollment is limited to clinical trial participants.\textsuperscript{94}

B. Charging for Investigational Drugs

1. Reasons for the Proposed Changes

FDA is proposing a number of significant changes to the current charging regulation. It cites three reasons for its proposal. First, when FDA adopted the current regulation in 1987, it did not anticipate that it would receive far more requests to charge for approved drugs that must be obtained from a third party than requests to charge for the sponsor's own drug.\textsuperscript{95} The proposed rule therefore provides criteria for charging for approved drugs in clinical trials. Second, the current regulation authorizes charging patients for treatment use only under a treatment IND or treatment protocol.\textsuperscript{96} The proposed rule therefore provides authority for charging under the two new categories of expanded access for treatment use. Third, the current regulation does not provide sponsors with clear guidance on the costs that can be recovered.\textsuperscript{97} The proposed rule therefore specifies the types of costs that can be recovered.

2. General Criteria for Charging

The proposed rule includes general criteria all sponsors would have to follow in order to charge for a drug in a clinical trial or for expanded access. Specifically, a sponsor would have to: (1) comply with the specific requirements that apply to the type of use for which charging is requested; (2) demonstrate that the amount to be charged reflects only those costs that are permitted to be recovered; and (3) obtain prior written authorization from FDA if charging for an investigational drug.\textsuperscript{98}

\textsuperscript{90} Id.; proposed 21 C.F.R. § 312.320(a).
\textsuperscript{91} Id.; proposed 21 C.F.R. § 312.320(c).
\textsuperscript{92} Id. at 75155.
\textsuperscript{93} Id.
\textsuperscript{94} Id. at 75155-75156.
\textsuperscript{95} Id. at 75169. An approved drug might be obtained from a third party, for example, to be used as an active control or in combination with the sponsor’s product.
\textsuperscript{96} Id.
\textsuperscript{97} Id. at 75169-70.
\textsuperscript{98} Id. at 75180; proposed 21 C.F.R. § 312.8(a)(1).
3. Criteria for Charging in a Clinical Trial

In the preamble to the proposed rule, FDA states that exceptional circumstances must exist to justify charging in a clinical trial.\textsuperscript{99}

a) Charging for a Sponsor’s Own Drug in a Clinical Trial

A sponsor that wishes to charge for its own drug in a clinical trial would have to: (1) provide evidence of a potential clinical benefit that would provide a significant therapeutic advantage over available products; (2) demonstrate that the data to be obtained are essential to establishing that the drug is safe or effective for initial approval or would support a significant labeling change; and (3) demonstrate that clinical development of the drug could not otherwise be continued, due to the extraordinary cost of the drug.\textsuperscript{100}

b) Charging for an Approved Drug Obtained from Another Entity for Use as an Active Control or in Combination with Another Drug

In an effort to address situations in which trial subjects receive therapy in place of a placebo because of ethical concerns,\textsuperscript{101} FDA proposes to allow charging for an approved drug obtained from another entity when used by the sponsor as an active control or in combination with another drug in a clinical trial designed to study the sponsor’s investigational drug.\textsuperscript{102} To obtain authorization, a sponsor would have to demonstrate that: (1) the trial is adequately designed to evaluate the safety or effectiveness of the sponsor’s drug, and (2) the drug is not being provided to the sponsor free of charge.\textsuperscript{103}

c) Charging for an Approved Drug Obtained from Another Entity for Clinical Testing

Finally, FDA proposes to allow sponsors of clinical trials to charge for an approved drug obtained from another entity for purposes of evaluation of that drug for another indication or for additional safety information.\textsuperscript{104} Typically, these sponsors are sponsor-investigators who do not conduct the research in question for commercial purposes and thus would not be able to recover the costs of obtaining the approved drug by marketing it.\textsuperscript{105} The sponsor would be required to demonstrate that: (1) the study is adequately designed to evaluate the safety or effectiveness of a new indication or to provide important safety information related to an approved indication, and (2) the drug is not being provided to the sponsor free of charge.\textsuperscript{106}

\textsuperscript{99} Id. at 75170.
\textsuperscript{100} Id. at 75180; proposed 21 C.F.R. § 312.8(b)(1)(i)-(iii).
\textsuperscript{101} Id. at 75171.
\textsuperscript{102} Id. at 75181; proposed 21 C.F.R. § 312.8(b)(2).
\textsuperscript{103} Id.; proposed 21 C.F.R. § 312.8(b)(2).
\textsuperscript{104} Id.; proposed 21 C.F.R. § 312.8(b)(3); see also id. at 75172.
\textsuperscript{105} Id. at 75172.
\textsuperscript{106} Id. at 75181; proposed 21 C.F.R. § 312.8(c).

FDA is also proposing to replace its current regulation that governs charging for investigational drugs provided under a treatment IND or protocol. By expanding the circumstances in which sponsors would be allowed to charge for investigational drugs provided for treatment use, FDA hopes to increase the availability of these drugs to patients with serious and life-threatening diseases with no alternative therapies.107

In any expanded access case, a sponsor requesting permission to charge would have to provide reasonable assurances to FDA that charging would not interfere with the development of the drug for marketing approval.108 Because FDA believes expanded access use under a treatment IND or protocol has more potential to interfere with drug development than individual patient access or intermediate-size patient population access,109 the agency would require additional assurances from sponsors of treatment INDs or protocols.110 These sponsors would have to provide evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval, demonstrate adequate progress in the development of the drug for marketing approval, and submit information under their general investigational plan specifying the drug development milestones they plan to meet in the coming year.111

Authorization to charge for expanded access for treatment use would last for one year (unless FDA specified a shorter period), but it could be renewed.112

5. Recoverable Costs

FDA also proposes to specify the kinds of costs a sponsor could recover when charging for an investigational drug in a clinical trial or for expanded access use.113 A sponsor could recover only the direct costs of making an investigational drug available.114 These are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery.115 They would include costs per unit to manufacture the drug, costs to obtain the drug from another manufacturing source, and costs to ship and handle the drug.116 They would not include expenditures to produce the drug for commercial sale, research and development, or administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.117

107 Id. at 75173.
108 Id. at 75181; proposed 21 C.F.R. § 312.8(c)(1).
109 Id. at 75172.
110 Id. at 75181; proposed 21 C.F.R. § 312.8(c)(2).
111 Id.; proposed 21 C.F.R. § 312.8(c)(2).
112 Id.; proposed 21 C.F.R. § 312.8(c)(3)-(4).
113 Id.; proposed 21 C.F.R. § 312.8(d).
114 Id.; proposed 21 C.F.R. § 312.8(d)(1)(i).
115 Id.; proposed 21 C.F.R. § 312.8(d)(1)(i).
116 Id.; proposed 21 C.F.R. § 312.8(d)(1)(i).
117 Id.; proposed 21 C.F.R. § 312.8(d)(1)(ii).
The proposed rule would allow sponsors who provide an investigational drug for treatment use for intermediate-size patient populations and larger patient populations under a treatment IND or protocol to recover costs associated with administering the program, as well as direct costs. These costs would include the cost of monitoring the IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with expanded access. In the preamble to the proposed rule, FDA states that it is not proposing to allow sponsors to charge for administrative costs for expanded access for individual patients because it believes these costs would be minor.

In all circumstances, sponsors would have to provide documentation supporting their calculation for cost recovery.

* * *

This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

<table>
<thead>
<tr>
<th>Name</th>
<th>Phone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard Kingham</td>
<td>202.662.5268</td>
<td><a href="mailto:rkingham@cov.com">rkingham@cov.com</a></td>
</tr>
<tr>
<td>Peter Safir</td>
<td>202.662.5162</td>
<td><a href="mailto:psafir@cov.com">psafir@cov.com</a></td>
</tr>
<tr>
<td>Michael Labson</td>
<td>202.662.5220</td>
<td><a href="mailto:mlabson@cov.com">mlabson@cov.com</a></td>
</tr>
<tr>
<td>Erika Lietzan</td>
<td>202.662.5165</td>
<td><a href="mailto:elietzan@cov.com">elietzan@cov.com</a></td>
</tr>
<tr>
<td>Grail Sipes</td>
<td>202.662.5379</td>
<td><a href="mailto:gsipes@cov.com">gsipes@cov.com</a></td>
</tr>
</tbody>
</table>

Covington & Burling LLP is one of the world’s preeminent law firms known for handling sensitive and important client matters. This alert is intended to bring breaking developments to our clients and other interested colleagues in areas of interest to them. Please send an email to unsubscribe@cov.com if you do not wish to receive future alerts.

© 2007 Covington & Burling LLP. All rights reserved.

---

118 [Id.; proposed 21 C.F.R. § 312.8(d)(2)].
119 [Id.; proposed 21 C.F.R. § 312.8(d)(2)].
120 [Id. at 75173].
121 [Id. at 75181; proposed 21 C.F.R. § 312.8(d)(3)].