Guidance for Industry

Expanded Access to Investigational Drugs for Treatment Use — Qs & As

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance is intended to provide information for industry, researchers, physicians, and patients about the implementation of FDA's regulations on expanded access to investigational drugs for treatment use under an investigational new drug application (IND) (21 CFR part 312, subpart I), which went into effect on October 13, 2009.[2] Since 2009, FDA has received a number of questions concerning its implementation of these regulations. As a result, FDA is providing guidance in a question and answer (Q & A) format, addressing the most frequently asked questions. In separate draft guidance,[3] FDA is providing its thinking on questions concerning its regulations on charging for investigational drugs under an IND (21 CFR 312.8), which also went into effect on October 13, 2009.[4] Information related to charging for investigational drugs made available under expanded access programs is in that draft guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
[2] 74 *Federal Register* 40900, August 13, 2009.
[3] Once finalized, the draft guidance on Charging for Investigational Drugs under an IND: Qs & As will represent the Agency's current thinking on this topic. The draft guidance is available on the Internet at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*. We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page.
[4] See also 74 Federal Register 40872, August 13, 2009.

II. BACKGROUND

FDA has a long history of facilitating access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives. In the past, FDA has been criticized for failing to clearly explain in regulations or guidance the range of IND mechanisms by which access could be obtained. Some concerns were that the lack of clarity resulted in disparate access for different types of patients, and access that was primarily limited to patients with certain diseases (i.e., cancers and HIV infection). To address these concerns, FDA revised its expanded access regulations in 2009. The revised regulations are intended to increase awareness and knowledge about expanded access programs and the procedures for obtaining investigational drugs for treatment use. FDA expected that increasing awareness about expanded access and the procedures for obtaining access should make investigational drugs more widely available in the appropriate situations.

Under FDA's current regulations, there are three categories of expanded access:

- Expanded access for individual patients, including for emergency use (21 CFR 312.310)
- Expanded access for intermediate-size patient populations (21 CFR 312.315)
- Expanded access for large patient populations under a treatment IND or treatment protocol (21 CFR 312.320)

The regulations also describe criteria that must be met to authorize expanded access, list requirements for expanded access submissions, and describe safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the drug.

III. QUESTIONS AND ANSWERS

Q1: What is expanded access for treatment use?

A1: The terms *expanded access*, *access*, and *treatment use* are used interchangeably to refer to use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The distinction between expanded access and the use of an investigational drug in the usual studies covered under an IND is that expanded access uses are not primarily intended to obtain information about the safety or effectiveness of a drug. Expanded access, access, and treatment use may also refer to use of an approved drug, where availability is limited by a risk evaluation and mitigation strategy (REMS), for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug through the REMS.

Expanded Access Submissions

Q2: What types of regulatory submissions can be used to obtain expanded access to a drug under the three expanded access categories?

A2: For each category of access, there are two types of regulatory submissions that can be used: (1) an access protocol submitted as a protocol amendment to an existing IND (i.e., an *access protocol*), or; (2) a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use (i.e., an *access IND*). 21 CFR 312.305(b)(1).

Q3: When should an access protocol submission be used?

A3: An access protocol submission should be used only if the sponsor seeking access has an existing IND in effect — typically, such a sponsor is a commercial sponsor with an existing IND under which the sponsor is developing the drug for marketing. When there is an existing IND in effect, FDA generally encourages the submission of an access protocol, rather than a new access IND, because having all access and clinical trial use consolidated under a single IND may facilitate earlier detection of safety concerns associated with a drug, and the administrative process is less burdensome for sponsors and FDA.

Q4: When should an access IND submission be used?

A4: An access IND submission generally should be used when: (1) there is no existing IND in effect for the drug, or; (2) there is an existing IND in effect for the drug, but the sponsor of the existing IND declines to be the sponsor of the access use (e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's physician submit a separate individual patient IND).

Q5: What information should be included in an access submission?

A5: An access submission must include all of the information required by 21 CFR 312.305(b) and any additional information required for the particular category of expanded access (described in § 312.310(b) for individual patient submissions, in § 312.315(c) for intermediate-size patient population submissions, and in § 312.320(b) for treatment submissions), either within the submission itself, or by relying on an existing IND.

FDA expects that an access protocol submission typically will include the information described in paragraphs 312.305(b)(2)(ii), (iii), (iv), and (viii) and 21 CFR 312.305(b)(3), and will rely on the data and information in the existing IND to satisfy the remaining requirements of 21 CFR 312.305(b). As noted above, the access protocol submission must also include the additional information that may be required for the specific category of access.

In some cases, an access IND submission will contain more information than an access protocol will, because there will be no existing IND on which to rely for the new access IND. However, when there is an existing IND for the drug but that sponsor has declined to be the sponsor of the access use, the sponsor of that existing IND may give the sponsor of the access IND permission to reference content in the existing IND to satisfy certain requirements for an access IND submission. FDA expects that reference to an existing IND typically may be used by an access IND sponsor to satisfy the requirements to submit the information described in 21 CFR 312.305(b)(v)(description of the manufacturing facility), 312.305(b)(vi) (chemistry, manufacturing, and controls information), and 312.305(b)(vii) (pharmacology and toxicology information). In cases in which an existing IND is referenced, FDA expects that submission of an access IND will not be significantly more burdensome than submission of an access protocol.

Q6: How does FDA categorize and sub-categorize access submissions for administrative purposes?

A5: For administrative purposes (e.g., tracking), FDA distinguishes between access INDs and access protocols, the different categories of access, as well as between emergency and non-emergency individual patient access. This results in the following 8 subcategories of access submissions:

(1) Individual patient IND (also referred to as a single patient IND)
(2) Individual patient protocol (also referred to as a single patient protocol)
(3) Emergency IND
(4) Emergency protocol
(5) Intermediate-size patient population IND
(6) Intermediate-size patient population protocol
(7) Treatment IND
(8) Treatment protocol

FDA recommends that the access submission identify the relevant subcategory.

Individual (or Single) Patient Access

Q6: Who can make a submission for individual patient expanded access when there is an existing IND for the drug?

A6: If there is an existing IND for the drug, either the sponsor of the existing IND or a licensed physician may make an individual patient expanded access submission (21 CFR 312.310(b)(1)).

The sponsor of the existing IND (e.g., a pharmaceutical company) can submit an individual patient access protocol to its existing IND. In this scenario, the sponsor of the

existing IND is also the sponsor of the access protocol, and the patient's physician is the investigator for the access protocol.

Alternatively, the sponsor of the existing IND can instead submit an individual patient access IND and cross-reference information in its existing IND to support the individual patient access IND. In this scenario, the sponsor of the existing IND is also the sponsor of the access IND, and the patient's physician is the investigator for the access IND.

In addition, a patient's physician can submit an individual patient access IND for his/her patient. In this scenario, when the patient's physician submits an access IND, the patient's physician is both the sponsor and the investigator -- in other words, he or she is considered a "sponsor-investigator." The physician may satisfy some of the access submission requirements by referring to information in the existing IND if the physician obtains permission from the sponsor of the existing IND to do so (see Q5 above). If the physician obtains this permission from the sponsor of the existing IND, the physician should provide FDA a letter of authorization from the sponsor of the existing IND that permits FDA to reference the sponsor's IND. If the sponsor of the existing IND does not authorize reference to the IND, the physician sponsoring the access IND must include in the IND all of the information required to support the access IND.

A patient's physician may not submit an individual patient access protocol to an existing IND for which the patient's physician is not the sponsor (see 21 CFR 312.30).

Because having all clinical trials and expanded access programs for a drug under a single IND may facilitate identification of safety concerns and ease the administrative burden for both sponsors and FDA, it is preferable for sponsors to submit an individual patient access protocol to an existing IND when possible.

Regardless of who is the sponsor of an individual patient access protocol or access IND, the patient can obtain access to the investigational drug only through a licensed physician (21 CFR 312.310).

Q7: What are the roles of the patient's physician and FDA in determining if access for an individual patient is appropriate?

A7: FDA may permit expanded access to a drug for an individual patient when the criteria in 21 CFR 312.305(a), applicable to all types of access, and the criteria in 21 CFR 312.310(a), specific to individual patient access, are met. For these criteria to be met, both the patient's physician and FDA must make certain determinations.

The patient's physician must determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition (§ 312.310(a)(1)). The patient's physician should make this determination based on the information about the drug available to the physician and the physician's knowledge of the patient's clinical situation.

As with all types of expanded access, FDA must determine, based on the information available to FDA, that the potential benefit justifies the potential risks of the treatment use with the drug and that those risks are not unreasonable in the context of the disease or condition to be treated (§ 312.305(a)(2)). In addition, to authorize the expanded access use, FDA must determine that the patient has a serious or life-threatening disease or condition and no other comparable or satisfactory therapeutic options ((§ 312.305(a)(1)), that providing access will not interfere with development of the drug for the expanded access use (§ 312.305(a)(3)), and that the patient cannot obtain the drug under another IND or protocol ((§ 312.310(a)(2))(e.g., in a clinical study of the drug).

Q8: When might it be appropriate to deny a request for individual patient access when previous requests for the same drug for the same or a similar use has been permitted?

A8: Each request for individual patient access to a drug should be treated as a unique clinical situation and the risks and benefits evaluated based on that clinical situation. Even when there are two (or more) individual patient access requests for patients with the same disease or condition, there may be significant differences in the clinical presentation of the disease or condition that make the risks acceptable for one patient, but not for another. For example, a patient may have a different stage of the disease or different tumor type than previous patients who were permitted access to the drug and, therefore, may have a different benefit/risk ratio. Similarly, a patient may have a co-morbid condition not present in previous patients who obtained access that would make the risk unacceptable. FDA may also become aware of new safety signals or information about effectiveness that change the benefit/risk ratio such that the risk is no longer acceptable for the patient. In cases such as these, access to additional patients might be denied.

There also may be nonclinical reasons for denying access. For example, a patient seeking access may be able to enroll in a clinical trial that was not accessible to a previous patient who was granted access (e.g., because the previous patient met criteria for exclusion from the trial or the trial was geographically inaccessible to the previous patient). FDA could also have become aware, since authorizing previous requests for access, that access is impeding the clinical development of the drug and, on that ground, deny further requests for access.

Q9: Under 21 CFR 312.310(c)(1), individual patient access is generally limited to a single course of therapy for a specified duration, unless FDA expressly authorizes multiple courses or chronic therapy. What does this mean for the treatment of a chronic condition?

A9: As reflected in 21 CFR 312.310(c)(1), FDA may authorize multiple courses of therapy or chronic therapy for individual patient access, including authorizing individual patient access to treat a chronic disease or condition that requires extended treatment. FDA generally authorizes such individual patient access when the circumstances of the treatment are well-defined and reasonable in light of the available evidence to support use of the drug. To fairly weigh the risks and benefits of a drug for use for individual patient access, FDA believes the planned course of therapy should be well-defined because it will usually be necessary to consider the planned dose and duration of therapy in relation

to what is known about the occurrence of toxicity for that dose and duration of therapy. Therefore, FDA typically authorizes access for an extended duration for the treatment of a chronic condition when the patient's condition and the information available about the safety of the drug support an extended duration of treatment, but does not typically authorize access of unspecified duration at the discretion of the treating physician. For example, FDA may authorize access of extended duration for a drug being developed to treat Multiple Sclerosis or other types of progressively debilitating neuromuscular disease if the drug must be administered chronically to slow the progression of the disease, and if the information available about the safety of the drug supports an extended duration of treatment. If access use is authorized for an extended duration, FDA may require the sponsor to monitor the individual patient access use (see 21 CFR 312.310(c)(3)).

Q10: Is Institutional Review Board (IRB) review and approval required for individual patient access uses?

A10: Under current FDA regulations, for all expanded access uses including individual patient access uses, investigators are required to ensure that IRB review and approval is obtained consistent with 21 CFR part 56 (21 CFR 312.305(c)(4)). 21 CFR part 56 requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of the IRB members are present ("full IRB review") (21 CFR 56.108(c)).

FDA is aware of concerns that this requirement for full IRB review may deter individual patient access to investigational drugs for treatment use. The concerns are primarily about IRB review of individual patient expanded access programs in settings in which IRB review is not readily accessible (e.g., healthcare settings that do not have IRBs). While patients seeking access may be in dire clinical circumstances, and thus may be an inherently vulnerable population for which ethical oversight is particularly important, we do not want to deter expanded access for individual patients. We have encouraged use of central IRBs for review of expanded access uses. However, other options may be needed, and FDA is currently considering whether other options might better facilitate individual patient expanded access while providing appropriate ethical oversight.

Q11: When should individual patient access using the emergency procedures in 21 CFR 312.310(d) be requested?

A11: Section 312.310(d) states that FDA may authorize expanded access for an individual patient without a written submission if there is "an emergency that requires the patient to be treated before a written submission can be made." The licensed physician or sponsor, however, must agree to submit an expanded access IND or protocol within 15 working days of FDA's authorization of the use (21 CFR 312.310(d)). FDA believes this regulation means that it is appropriate to request individual patient access using the emergency procedures described in 21 CFR 312.310(d) when treatment of the patient must occur within a very limited number of hours or days. FDA intends to scrutinize

emergency requests and to authorize access for such requests only when the situation is a true emergency.

Q11: Can the same drug be used in an emergency situation at the same institution more than once? If so, is prospective IRB review required for the subsequent expanded access emergency use?

A11: There can be more than one expanded access emergency use of the same drug at the same institution. FDA expects that, for expanded access uses authorized under the emergency procedures, there typically will not be time to obtain prior IRB approval of the use. In such cases, the emergency use must be reported to the responsible IRB within 5 working days of initiation of treatment (21 CFR 56.104(c)). Once an investigational drug is used in an emergency situation without prior IRB approval, any subsequent uses of the investigational drug at that same institution would ordinarily require prior IRB review and approval (21 CFR 56.104(c)). However, when prior IRB review and approval is not feasible for a subsequent expanded access emergency use at a particular institution, FDA does not intend to deny the subsequent request for emergency use due to lack of time to obtain prospective IRB review, as long as that use will be reported to the IRB within 5 working days of initiation of treatment.

Intermediate-Size Patient Population and Treatment INDs and Protocols

Q12: Can there be more than one intermediate-size patient population access program for a particular drug for the same disease or condition?

A12: When multiple patients with the same disease or condition seek access to a particular drug, and the relevant criteria for access are met, FDA believes that it is generally most efficient to consolidate access in a single intermediate-size patient population IND or protocol. If the drug is being developed, FDA believes it is most efficient if the company that is developing the drug for marketing is the sponsor of the single intermediate-size patient population access program. However, the regulations do not preclude the possibility of authorizing more than one intermediate-size patient population access program, with different sponsors or sponsor-investigators, for a drug for the same disease or condition. Thus, there may be situations in which there are multiple intermediate-size patient population access programs for a drug for the treatment of the same disease or condition. FDA expects these situations to arise infrequently.

Q13: When is it appropriate to request access for multiple patients using an intermediate-size patient population access IND or protocol rather than a treatment IND or protocol?

A13: Intermediate-size patient population access programs are intended generally to accommodate population sizes smaller than the large populations typical of treatment INDs or protocols (hundreds to thousands of patients) and larger than the limited number

of patients who might obtain access under individual patient INDs or protocols. When the requested drug is being developed, intermediate-size patient population access programs generally are used earlier in drug development than treatment INDs or protocols. Also, in contrast to a treatment IND or protocol, an intermediate-size patient population access program can be used to obtain access to a drug that is not being developed (21 CFR 312.315(a)(1)), or to an approved or related drug that is not available through marketing channels (21 CFR 312.315(a)(3)).

When Can Treatment Begin Under an Access IND or Protocol?

Q17: When can emergency use access begin?

A17: For an emergency use, access to the drug may begin upon verbal authorization (usually over the telephone) by the reviewing FDA official (21 CFR 312.305(d)(2)(i)). As explained in the response to Q12 above, FDA expects that, for expanded access uses authorized under the emergency procedures, there typically will not be time to obtain prior IRB approval of the use. In such cases, the emergency use must be reported to the responsible IRB within 5 working days of initiation of treatment (21 CFR 56.104(c)).

Q18: When can treatment begin under access INDs not for emergency use?

A18: When an access IND (not for emergency use) is submitted, the treatment use of the drug may begin when the IND goes into effect and IRB approval has been obtained consistent with 21 CFR part 56 (see 21 CFR 312.305(c)(4)). As is true for any new IND, an access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA (21 CFR 312.40 and 312.305(d)(1)).

Q19: When can treatment begin under access protocols not for emergency use?

A19: For an individual patient or intermediate-size patient population access protocol, access to the drug can begin once the access protocol has been submitted to FDA and has been approved by an IRB (21 CFR 312.305(d)(2)). For a treatment protocol, however, access may not begin until 30 days after FDA receives the protocol or on earlier notification by FDA (21 CFR 312.305(d)(2)(ii)), and IRB approval has been obtained consistent with 21 CFR part 56 (see 21 CFR 312.305(c)(4)).

General Questions

Q16. In general, how does FDA determine that authorizing expanded access to a drug will not interfere with clinical trials or drug development?

A16. Under 21 CFR 312.305(a)(3), to authorize any category of expanded access, FDA must determine that access to the drug for the requested use will not interfere with the

initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use, or otherwise compromise the potential development of the drug for the expanded access use. For all categories of access, sponsors are required to include in their access submissions information adequate to demonstrate that access to the drug will not interfere with clinical investigations or drug development, among other information (21 CFR 312.310(b), 312.315(c), 312.320(b)). FDA believes that expanded access programs that treat larger patient populations generally have the greatest potential for interfering with clinical investigations or drug development, because of such programs' greater potential to interfere with recruiting patients for the clinical investigation(s). FDA typically determines whether an expanded access program will interfere with clinical investigations or drug development based on the information provided by the sponsor in its access submission; if the information provided by the sponsor is not adequate for FDA to make this determination, FDA may ask the sponsor for additional information. For example, before authorizing a treatment IND for a drug for which clinical trials are ongoing, FDA may ask the sponsor to explain how the sponsor will ensure that the treatment IND will not interfere with accrual of patients in the clinical trials, and how the sponsor will determine whether interference is occurring, if such information is not provided in the access submission. More specifically, FDA may ask the sponsor to submit to its IND a comprehensive investigational plan with a timetable and milestones (if it has not done so already), so that FDA can periodically assess whether the treatment IND is affecting accrual of patients in the clinical trials or other parameters related to the pace of drug development. If FDA then determined that the ongoing treatment IND was interfering with clinical trials or drug development, or that the sponsor was not pursuing marketing approval for the expanded access use with due diligence, FDA could place the treatment IND on clinical hold (21 CFR 312.42(b)(3)).

Q14: Might FDA consider an IND or protocol submission an access submission and identify and review it as such, even though the applicant does not identify it as an access submission?

A15: Yes. For example, FDA intends to evaluate whether proposals for studies described as open-label safety studies should be considered treatment INDs or protocols. The goal of an open-label safety study is to better characterize the safety of a drug late in its development. However, in practice, many studies that are described as open-label safety studies have characteristics that appear to be more consistent with treatment INDs or protocols. If a protocol or IND describes an open-label study that provides for broad access to an investigational drug in the later stages of development, but lacks planned, systematic data collection, and a design adequate to meaningfully evaluate a safety issue, FDA will generally consider the submission to be a treatment IND or protocol. In the event that a protocol is not submitted as an access protocol, but is designated as such by FDA, the review division will notify the sponsor of the designation.

Q20. Can FDA require a company to provide expanded access to its drug if FDA authorizes the expanded access?

A20. No, FDA cannot compel a company to provide expanded access to its drug. When a company provides expanded access to its drug, it is doing so voluntarily.

Q21: May treatment with 2 drugs be requested and authorized under a single access program (under a single access IND or protocol) or may an individual patient participate in more than 1 access program (e.g., be enrolled in 2 different treatment INDs)?

A21: Yes, a single access program may involve treatment with more than 1 investigational drug, and a patient may be enrolled in more than 1 access program. When access to 2 or more investigational drugs is needed to treat a single disease and the relevant criteria are met, FDA believes that it is most efficient to provide access to the 2 investigational drugs under a single access program, rather than to provide access by having a patient enroll in 2 separate access programs (one for each drug), because management of the patient's disease and treatment, and the collection of information about the therapy, is likely to be better coordinated under a single access program.