
Charging for Investigational Drugs Under an IND — Questions and Answers Guidance for Industry

**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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Procedural**

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Guidance for Industry

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Charging for Investigational Drugs Under an IND — Questions and Answers Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information for industry, researchers, physicians, institutional review boards (IRBs), and patients about the implementation of FDA's regulation on charging for investigational drugs² under an investigational new drug application (IND) for the purpose of either clinical trials or expanded access for treatment use (21 CFR 312.8), which went into effect on October 13, 2009.³ Since 2009, FDA has received a number of questions concerning its implementation of the charging regulation. As a result, FDA is providing guidance in a question and answer format, addressing the most frequently asked questions. In a separate guidance,⁴ FDA provides answers to questions concerning regulations on expanded access to investigational drugs for treatment use (21 CFR part 312, subpart I), which also went into effect on October 13, 2009. Also in a separate guidance, FDA describes Form FDA 3926 (Individual Patient Expanded Access--Investigational New Drug Application (IND)) and the process for submitting expanded access requests for individual patient INDs.⁵

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² For the purposes of this guidance, the terms *investigational new drug*, *investigational drug*, *drug*, and *drug product* refer to both human drugs and biological products regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research.

³ *Federal Register* of August 13, 2009 (74 FR 40872).

⁴ See the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers* for the Agency's current thinking on this topic. We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the FDA guidance Web page at <http://www.fda.gov/RegulatoryInformation/Guidances/>.

⁵ See the guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* for the Agency's current thinking on this topic.

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In general, FDA's guidance documents 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.

II. BACKGROUND

For many years, FDA authorized charging for an investigational drug under a regulation that was published in 1987 (the 1987 charging rule) (52 FR 19466, May 22, 1987). In 2009, FDA revised its 1987 charging rule for three principal reasons: (1) to take into account circumstances concerning charging for investigational drugs in a clinical trial that were not anticipated when the rule was written, (2) to set forth criteria for charging for investigational drugs made available under all categories of expanded access described in the expanded access regulations that were also revised in 2009, and (3) to specify the types of costs that can be recovered when charging for an investigational drug under an IND.

The revised charging regulation provides the following:

- General criteria for authorizing charging for an investigational drug (21 CFR 312.8(a))
- Criteria for charging for an investigational drug in a clinical trial (21 CFR 312.8(b))
- Criteria for charging for an investigational drug for an expanded access use under 21 CFR part 312, subpart I (21 CFR 312.8(c))
- Criteria for determining what costs can be recovered when charging for an investigational drug (21 CFR 312.8(d))

III. QUESTIONS AND ANSWERS

A. General Questions

Q1: How much time does FDA have to review and respond to a request to charge for an investigational drug?

A1: The provision in 21 CFR 312.8 does not specify a time frame for FDA to respond to a request to charge for an investigational drug. However, FDA intends to respond to charging requests within 30 days of receipt when possible.

Q2: Under 21 CFR 312.8, who requests authorization from FDA to charge for an investigational drug for use under an IND?

A2: Section 312.8 permits only the sponsor of the IND to request FDA's authorization to charge for an investigational drug for use under the IND (§ 312.8(a)). The sponsor of the IND is not always the manufacturer of the drug. For example, if the manufacturer of an unapproved drug is

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not the sponsor of the IND under which the drug will be used, the manufacturer is not required to obtain authorization from FDA to charge the sponsor of the IND for the unapproved drug. However, in such a situation, if the sponsor wants to charge patients to recover the cost charged by the manufacturer, the sponsor must obtain FDA's written authorization before it can begin charging patients (§ 312.8(a)(3)).

Q3: Once FDA authorizes a request to charge, whom may the sponsor charge?

A3: Although FDA determines whether a sponsor may charge for an investigational drug used in a clinical trial or for expanded access, FDA does not decide *how* that charging is to be carried out. FDA anticipates that the sponsor would ordinarily charge a patient directly or would charge a third-party payer if reimbursement were available. FDA notes that it has no authority to require that the Centers for Medicare and Medicaid Services reimburse for investigational drugs for which FDA has authorized charging. Similarly, FDA has no authority to dictate reimbursement policy to any other entity, including private health insurance providers. For questions pertaining to third-party payer reimbursement, the third-party payer should be consulted.

B. Charging in Clinical Trials

Q4. When a sponsor uses its own investigational drug in a clinical trial, what requirements must the sponsor satisfy to charge for the drug?

A4: When a sponsor is using its own investigational drug, including an investigational use of its approved drug, in a clinical trial, a sponsor must do *all* of the following to obtain authorization to charge for the drug:

- Provide evidence to FDA that the drug has a potential clinical benefit that, if demonstrated in clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition (21 CFR 312.8(b)(1)(i)).
- Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval, or would support a significant change in the labeling of an approved drug (e.g., a new indication, inclusion of comparative safety information) (§ 312.8(b)(1)(ii)).
- Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor (§ 312.8(b)(1)(iii) (see also Q5 regarding extraordinary cost)).
- Provide documentation to support its calculation for cost recovery to show that the calculation is consistent with the requirements of § 312.8(d)(1). The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculation (§ 312.8(d)(3)).

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Sponsors must meet *all* of these requirements and must obtain written authorization from FDA to charge before they begin to charge for an investigational drug (§ 312.8(a)(3)).

Q5: What constitutes *extraordinary cost*?

A5: As noted in A4, 21 CFR 312.8(b)(1)(iii) requires that the sponsor demonstrate that it could not conduct the clinical trial without charging for the investigational drug because the cost of the drug is extraordinary to the sponsor. Section 312.8(b)(1)(iii) also describes the reasons that the cost of a drug may be extraordinary. The cost of a drug may be considered extraordinary to a sponsor because of manufacturing complexity, scarcity of a natural resource, the large quantity of the drug needed (e.g., based on the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor) (§ 312.8(b)(1)(iii)).

Q6: Does FDA consider the financial resources available to a sponsor when determining whether the cost of providing its investigational drug in a clinical trial is extraordinary?

A6: Yes. The provision in 21 CFR 312.8(b)(1)(iii) describes the reasons that the cost of a drug might be extraordinary *to the sponsor*, including the resources available to a sponsor. For example, a cost that is considered extraordinary to a small start-up company may not be considered extraordinary to a large established company.

Q7: What is an independent certified public accountant?

A7: An independent certified public accountant is a certified public accountant who is not an employee of the company seeking to charge for an investigational drug.

Q8: When a company is the sponsor of a clinical trial evaluating an unapproved use of its approved drug, is the company required to obtain authorization to charge for its drug?

A8: Yes. In accordance with 21 CFR 312.8(b)(1), a sponsor of a clinical trial must obtain authorization to charge for its own drug, including investigational uses of its approved drug.

Q9: If a sponsor (e.g., a physician-researcher who is a sponsor-investigator) purchases an approved drug from the company that markets the drug or another commercial distribution entity (e.g., a pharmacy or a wholesaler) for use in a clinical trial, is the sponsor required to obtain authorization from FDA to charge for the approved drug?

A9: No. If a sponsor is not the company that markets the approved drug and the sponsor must purchase the approved drug for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug or for use of the approved drug as an active control) or as concomitant therapy, the sponsor is not required to obtain FDA authorization to charge for the approved drug (see 21 CFR 312.8(a)(1)).

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Q10: If a sponsor's own approved drug is used as concomitant therapy for an approved use during a clinical trial intended to evaluate another drug, should the sponsor obtain authorization to charge for the drug used as concomitant therapy?

A10: No. In many clinical trials, approved drugs are used as concomitant therapy for subjects during the trials, but are not part of the clinical trial evaluation. For example, (1) patients may be required by a protocol to take certain approved drugs as concomitant therapy before or during the trial (e.g., patients may receive antihistamines for immune response concerns in a clinical trial to study a recombinant protein, in order to mitigate potential risks of participation in the trial; or all patients may receive concomitant therapy before randomization to either the investigational drug or placebo) or (2) patients may be permitted by the protocol to continue taking certain approved drugs as concomitant therapy during the trial because such drugs are not likely to interact with the study drug(s) or otherwise confound the results of the trial (e.g., pain medications for patients in a clinical trial to study a drug intended to treat cancer) or because discontinuing the drug might adversely affect the patient.

In accordance with 21 CFR 312.8(b)(1), a sponsor must obtain prior authorization from FDA to charge for its investigational drugs, including investigational uses of its approved drugs. However, FDA regulations do not require a sponsor to obtain prior authorization to charge for its own approved drug when that drug is used as concomitant therapy for an approved use and is not part of the clinical trial evaluation.

Q11: How can a sponsor charge for its investigational drug in a blinded, controlled clinical trial without compromising the blind and therefore the integrity of the clinical data generated from the trial?

A11: FDA recognizes that in certain situations, charging for an investigational drug in a clinical trial may have the potential to compromise the blinding of study subjects to which therapy they have received (e.g., in a situation in which subjects who are in the treatment arm of the study are charged, and subjects who are in the control arm are not charged). However, FDA believes that there are methods for preserving the blind that sponsors could use in most cases. We are not providing hypothetical examples because we anticipate that the method for preserving the blind will be unique to each study design. When these situations arise, the sponsor may seek advice from the appropriate review division in the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER) or from the review office in the Center for Biologics Evaluation and Research (CBER) on how to preserve the blind, based on the specifics of the given situation. To find the appropriate CDER OND review division, see <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm>. For contact information for CBER, see <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm>.

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Q12: How long may a sponsor charge for an investigational drug in a clinical trial after FDA authorizes the charging?

A12: Charging may continue for the entire length of the clinical trial unless FDA specifies a shorter duration (21 CFR 312.8(b)(2)).

C. Charging For Expanded Access Use

Q13: What requirements must a sponsor satisfy to charge for expanded access use?⁶

A13: The sponsor of an expanded access IND or protocol must do *all* of the following to obtain authorization to charge for the drug:

- Provide reasonable assurance to FDA that charging will not interfere with drug development (21 CFR 312.8(c)(1)).
- Provide documentation in its charging request submission to show that its calculation of the amount to be charged is consistent with the requirements in § 312.8(d). This documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculation (§ 312.8(d)(3)). Documentation of the calculation of the amount to be charged for a drug obtained from another source could consist of a copy of the receipt or invoice from the source that provided the drug to the expanded access sponsor.

For expanded access under § 312.320 (treatment IND or treatment protocol), the reasonable assurance that charging will not interfere with drug development must include (1) evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned; (2) evidence of adequate progress in the development of the drug for marketing approval; and (3) information submitted under the general investigational plan specifying the drug development milestones the sponsor plans to meet in the next year (§ 312.8(c)(2)).

Sponsors of expanded access INDs and protocols must meet these requirements and obtain written authorization from FDA before they begin to charge for an investigational drug (§ 312.8(a)(3)).

Q14: How long may a sponsor charge for an investigational drug for expanded access use after FDA authorizes the charging?

A14: Charging for an investigational drug for expanded access use may continue for 1 year from the time of FDA authorization unless FDA specifies a shorter period (21 CFR 312.8(c)(4)). FDA periodically reassesses whether charging is interfering with development of a drug for marketing

⁶ The regulations regarding expanded access to investigational drugs for treatment use are in 21 CFR part 312, subpart I. As explained in footnote 4, FDA's guidance for industry *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers* provides information on expanded access.

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and believes that the 1-year anniversary is typically a reasonable point in time to reevaluate charging requests. FDA may reauthorize charging for an investigational drug for expanded access use for additional periods. If a sponsor wishes to continue charging beyond the expiration of the existing authorization, FDA recommends that the sponsor submit a request to reauthorize charging at least 60 days prior to the expiration of the existing authorization to charge for the investigational drug.

Q15: What must a sponsor do to obtain authorization to continue charging for an investigational drug for expanded access use beyond the duration of its existing charging authorization (i.e., for additional periods)?

A15: If a sponsor wishes to continue charging beyond the duration of its existing charging authorization, the sponsor must submit a request to FDA for reauthorization to charge for the investigational drug (21 CFR 312.8(c)(4)). The request must satisfy the same requirements as the initial request for charging authorization (see Q13). It is also helpful for sponsors to specify whether any information from the original or previous request has changed. The sponsor must receive written reauthorization from FDA before it can continue to charge for the investigational drug beyond the period previously authorized (21 CFR 312.8(a)(3)).

D. Cost Recovery Calculations

Q16: What costs can a sponsor recover when charging for an investigational drug in a clinical trial?

A16: A sponsor can only recover the direct costs of making a drug available to subjects in a clinical trial — that is, those costs that are specifically and exclusively attributable to providing the drug to clinical trial subjects (21 CFR 312.8(d)(1)). These include costs to manufacture the drug in the quantity needed to conduct the clinical trial for which charging has been authorized or costs to acquire the drug from another source, including costs to ship and handle (e.g., store) the drug.

Q17: What costs can a sponsor recover when charging for an investigational drug for expanded access use under 21 CFR part 312, subpart I?

A17: When charging for individual patient expanded access (under § 312.310) to an investigational drug, a sponsor may recover only its direct costs associated with making the drug available to the patient (see Q16 and § 312.8(d)). For individual patient expanded access, the sponsor may not charge for indirect costs, including administrative costs associated with providing an investigational drug. Examples of indirect costs include:

- Costs associated with developing the treatment protocol and informed consent document
- Costs associated with corresponding with the IRB, FDA, and/or the drug manufacturer
- Costs associated with reporting to the IRB and/or FDA
- IRB fees and expenses

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When charging for an investigational drug used in an intermediate-size patient population expanded access IND or protocol (under § 312.315) or a treatment IND or protocol (under § 312.320), in addition to the direct drug costs, a sponsor may recover the cost of (1) monitoring the expanded access IND or protocol, (2) complying with IND reporting requirements, and (3) other administrative costs directly associated with the expanded access use (§ 312.8(d)(2)).

Q18. May the sponsor of an expanded access IND or protocol recover the cost of the fees the sponsor pays to a third party for administering an intermediate-size patient population expanded access IND or protocol or a treatment IND or protocol?

A18: Yes. FDA interprets 21 CFR 312.8(d)(2) as permitting the sponsor of an expanded access IND or protocol to recover the cost of the fees paid to a third party for administering an intermediate-size patient population or treatment IND or protocol, including any profit for the third party that may be included in the fees. The fees paid to the third party should be included in the calculation for cost recovery that the sponsor provides in its request to charge.

Q19. Does a sponsor need FDA authorization to charge for the costs of drug delivery, including the costs associated with formulation, packaging, instrumentation, monitoring, disposables, setup, and nursing care?

A19: No. The provision in 21 CFR 312.8(d)(1) is intended to permit a sponsor to recover the direct costs incurred in making a drug available from the onset of manufacturing to the point it arrives at the destination to which it was shipped or, for a drug acquired from another source as a finished product (e.g., when manufacturing is outsourced), acquisition, shipping, and handling costs for the drug. Recovery of subsequent costs incurred at a clinical trial site (e.g., a hospital or clinic), including pharmacy costs (e.g., the cost to reconstitute a drug for infusion), nursing costs (e.g., costs associated with administering a drug and monitoring study subjects), equipment costs (e.g., intravenous administration sets, infusion pumps), and costs for study-related procedures (e.g., chemistry labs, radiographic procedures), do not fall within the scope of § 312.8. In other words, FDA authorization is not needed for a sponsor to recover those costs.

Q20: What information is a sponsor required to submit to support its cost calculation?

A20: Under 21 CFR 312.8(d)(3), to support its calculation of recoverable costs, a sponsor must provide documentation to show that its calculation is consistent with the requirements of § 312.8(d)(1), describing recovery of direct costs and, if applicable, the requirements of § 312.8(d)(2), describing certain additional costs that may be recovered for intermediate-size patient population expanded access uses or treatment INDs or protocols. This documentation must be accompanied by a statement that an independent, certified public accountant has reviewed and approved the calculations (§ 312.8(d)(3)).