Charging for Investigational Drugs Under an IND Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Dat Doan, 240-402-8926, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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Center for Biologics Evaluation and Research (CBER)
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Charging for Investigational Drugs Under an IND Questions and Answers Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 regulations on charging for investigational drugs[2] 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 issued the final guidance for industry *Charging for Investigational Drugs Under IND — Questions and Answers* (June 2016) providing recommendations in a question-and-answer format, addressing the most frequently asked questions.

When finalized, this guidance will replace the 2016 guidance. Significant changes to the 2016 version include additional recommendations related to the need for submission of a statement by an independent certified public accountant under certain circumstances, and distribution of the manufacturing, administrative, or monitoring costs from the first year over the expected duration of the expanded access IND or protocol.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Office of Clinical Policy (OCLiP), and the Oncology Center for Excellence (OCE) and in consultation with the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] In this guidance, the terms *investigational new drugs, investigational drugs, drugs*, and *drug products* refer to both human drugs and biological drug products regulated by CDER or CBER.

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

In separate guidance documents, FDA provides answers to questions concerning regulations on expanded access to investigational drugs for treatment use (21 CFR part 312, subpart I)[4] and discusses 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]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance 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 (§ 312.8(a))
- Criteria for charging for an investigational drug in a clinical trial (§ 312.8(b))
- Criteria for charging for an investigational drug for an expanded access use under part 312, subpart I (§ 312.8(c))
- Criteria for determining what costs can be recovered when charging for an investigational drug (§ 312.8(d))

[4] See the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (June 2016/updated October 2017) for the Agency's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] See the guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* (June 2016/updated October 2017) for the Agency's current thinking on this topic.

The questions and answers in this guidance are organized as follows: (A) General Questions Related to Charging for Clinical Trials and Expanded Access Use, (B) Charging in Clinical Trials, (C) Charging for Expanded Access Use, and (D) Cost Recovery Calculations.

III. QUESTIONS AND ANSWERS

A. General Questions Related to Charging for Clinical Trials and Expanded Access Use

Q1. How much time does FDA have to review and respond to a sponsor's request to charge for an investigational drug?

The provision in § 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?

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)). Often the manufacturer of the investigational drug is the sponsor of the IND under which clinical studies of the investigational drug are conducted or under which the investigational drug is provided for treatment use under expanded access. However, this is not always the case. When the sponsor of an IND is a person or entity other than the manufacturer of the investigational drug (e.g., a physician), the IND sponsor, and not the drug manufacturer, must obtain FDA's prior written authorization to charge patients for the investigational drug under that IND (§ 312.8(a)(3)). See Q8 and Q9 for further information on charging for approved drugs for investigational use.[6]

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

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 payor if reimbursement is available. FDA notes that its authorities do not extend to reimbursement policy or reimbursement decisions for investigational drugs for which FDA has authorized charging, including those made by entities such as third-party payors. For questions pertaining to third-party payor reimbursement, the third-party payor should be consulted. FDA advises sponsors to ensure that charging for drugs in clinical trials or expanded access use does not create barriers to access that may exacerbate disparities in clinical trial participants or expanded access patients.

[6] In this guidance, the term *approved drugs* refers to drugs approved by FDA.

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?

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* 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 (§ 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 the extent applicable, 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)).

Sponsors must meet *all* 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*?

As noted in the answer to Q4, § 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. 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?

Yes. The provision in § 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?

An independent certified public accountant should be a certified public accountant who is qualified to make the required determinations for charging and not an employee of the company or institution 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?

Yes. In accordance with § 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. The sponsor can recover only the cost allowed under the regulations in § 312.8(d)(1), that is, the direct cost of providing the drug for the investigational use for which FDA has authorized cost recovery. The direct cost of providing the drug may not necessarily be the same as the market price of the approved product used for an approved indication (also see Q16 regarding direct cost).

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 from 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?

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, 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 § 312.8(a)(1)).

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, is the sponsor required to obtain authorization to charge for the drug used as concomitant therapy?

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:

- 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).

- 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 § 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 (i.e., the approved drug itself is not being evaluated for an investigational use).

Q11. 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?

FDA recognizes that charging for an investigational drug in a clinical trial may have the potential to compromise the blinding of study participants to which therapy they have received (e.g., in a situation in which participants who are in the treatment arm of the study are charged, and participants who are in the control arm are not charged). 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 appropriate 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 https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information.

- For contact information for CBER, see https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/cber-offices-divisions.

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

Charging may continue for the entire length of the clinical trial unless FDA specifies a shorter duration (§ 312.8(b)(2)). Refer to Q14 for information about how long a sponsor may charge for an investigational drug for expanded access use.

C. Charging for Expanded Access Use

Q13. What requirements must a sponsor satisfy to charge for expanded access use?[7]

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

- Provide reasonable assurance to FDA that charging will not interfere with drug development (§ 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), to the extent applicable. This documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculation (§ 312.8(d)(3)). When the amount to be charged for a drug is simply the amount charged to the expanded access sponsor by a third party who provides the drug to the expanded access sponsor, such that there is no calculation of cost made by the sponsor to which the requirement under § 312.8(d)(3) applies, the expanded access sponsor should provide a copy of the receipt or invoice from the source that provided the drug to the expanded access sponsor to justify the amount to be charged for the drug.

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 or trials 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?

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 (§ 312.8(c)(4)). FDA periodically reassesses whether charging is interfering with development of a drug for marketing and believes that the 1-year anniversary is typically a reasonable point in time to reevaluate charging requests. Additionally, FDA may reauthorize charging for an investigational drug for expanded access use for additional periods (typically a year or shorter based on the request and

[7] The regulations regarding expanded access to investigational drugs for treatment use are in 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* (June 2016/updated October 2017) provides information on expanded access.

the circumstances) under § 312.8(c)(4) if reauthorization is requested by the sponsor and all criteria are met. 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 (see Q15).

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)?

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 (§ 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 (§ 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?

A sponsor can recover only 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 for which FDA has authorized cost recovery (§ 312.8(d)(1)). These include costs to manufacture the drug, including manufacturing at the site of drug delivery (e.g., raw materials, labor, non-reusable supplies and equipment used 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, and direct costs to ship and handle (e.g., store) the drug (§ 312.8(d)(1)(i)).

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

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 administrative costs associated with providing an investigational drug (§ 312.8(d)(1)(ii)).

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 (1) the cost of monitoring the expanded access IND or protocol; (2) the cost of 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?

Yes. FDA interprets § 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. In addition, FDA recommends that the sponsor disclose to the patients any relationship it may have with the third party. If any costs may be the responsibility of the patient, this information must be included in the informed consent document, per § 50.25(b)(3).

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

No. The provision in § 312.8(d)(1) is intended to permit a sponsor to recover the direct costs incurred in making a drug available. FDA authorization is not needed to recover 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) because these costs do not fall within the scope of § 312.8.

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

Under § 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)).

Q21. Is a sponsor of an expanded access IND who seeks to recover the cost incurred from obtaining an investigational drug from another source required to include in the charging request submitted to FDA a statement that an independent certified public accountant has reviewed and approved the calculation?

No. As discussed in the response to Q13, when the amount to be charged for a drug is simply the amount charged to the expanded access sponsor by a third party who provides the drug to the expanded access sponsor, such that there is no calculation of cost made by the sponsor for an

independent certified public accountant to approve and to which the requirement under § 312.8(d)(3) applies, the expanded access sponsor should provide a copy of the receipt or invoice from the source that provided the drug to the expanded access sponsor to justify the amount to be charged for the drug.

Q22. Can a sponsor of an intermediate or treatment IND or protocol seeking to charge for the investigational drug distribute the costs associated with monitoring the program for the intermediate or treatment IND or protocol and other administrative "startup" costs over the expected duration of the IND or protocol, rather than in the first year of the treatment?

Yes. The costs associated with monitoring the program for an intermediate or treatment IND and other administrative startup costs may be higher in the first year and may be expected to decrease in subsequent years. If all the additional costs in the first year are charged to the patients who will be receiving the drug in the first year, they may have to pay a higher price for the drug compared to patients receiving it in subsequent years. The sponsor may prefer to distribute these costs to all patients who are expected to participate in the IND or protocol, rather than among first-year patients, to reduce the per patient cost difference between patients treated earlier and patients treated later.

Such a cost distribution plan may be authorized. The cost amortization for such a cost distribution plan should be done in accordance with standard accounting practices, and the calculations for cost recovery must be reviewed and approved by an independent certified public accountant (§ 312.8(d)(3)). Regardless of whether an amortization plan is included in the request and approval to charge, the charging authorization still expires no later than 1 year from authorization and sponsors must still submit a request to reauthorize charging if they wish to continue charging after the expiration of the initial authorization period (§ 312.8(c)(4)).

Q23. Can a sponsor of an expanded access IND or protocol seeking to charge for the investigational drug distribute the higher manufacturing costs associated with manufacturing the drug in the first year compared to subsequent years, over the duration of the IND or protocol, rather than in the first year of the treatment?

Yes. The costs of manufacturing a drug in the first year are often expected to be higher compared to subsequent years. If all the additional costs of setting up the manufacturing process in the first year are charged to the patients who will be receiving the drug in the first year, they may have to pay a higher price for the drug compared to patients receiving it in subsequent years. The sponsor may prefer to distribute one-time costs associated with setting up the manufacturing process among all patients who are expected to participate in the IND or protocol, rather than among first-year patients, to reduce the per patient cost difference between patients treated earlier and patients treated later.

Such a cost distribution plan may be authorized. The cost amortization for such a cost distribution plan should be done in accordance with standard accounting practices, and the calculations for cost recovery must be reviewed and approved by an independent certified public accountant (§ 312.8(d)(3)). Regardless of whether an amortization plan is included in the request

and approval to charge, the charging authorization still expires no later than 1 year from authorization and sponsors must still submit a request to reauthorize charging if they wish to continue charging after the expiration of the initial authorization period (§ 312.8(c)(4)).