FDA Issues Draft Guidance on Financial Disclosure by Clinical Investigators

By Katherine R. Leibowitz

On 24 May 2011, the US Food and Drug Administration (FDA) released draft guidance to replace its current guidance on disclosure of financial interests held by clinical investigators.[1] The draft guidance reflects the changing landscape both within and outside FDA regarding transparency of financial interests. Consistent with increased public attention to physician-industry financial ties, the tenor of the draft guidance suggests that clinical trial sponsors should expect a more rigorous review by FDA of these financial arrangements. Comments on the draft guidance must be submitted by 25 July 2011.

This article highlights the main changes proposed by the draft guidance that sponsors should consider as they select clinical trial investigators, design their studies and prepare the financial disclosure information to be submitted in the marketing applications to FDA.

Background

The financial disclosure regulations at 21 CFR 54 are designed to help uncover potential investigator bias that may arise due to financial ties between the investigator and the clinical trial sponsor. When submitting marketing applications that contain clinical data, applicants (typically the study sponsor) must either certify the absence of certain financial interests of the investigators or disclose those interests and explain steps taken to minimize the potential for bias. The existing guidance was published in 2001[2] and, along with the new draft guidance, is intended to assist sponsors, applicants, investigators and FDA staff in interpreting and complying with the financial disclosure regulations.

The newly released draft guidance addresses recommendations made in a 2009 Office of the Inspector General (OIG) report about FDA oversight of investigators' financial information, and answers questions FDA has received from industry and the public. The draft guidance reorganizes and includes almost all of the content of the current guidance, expands upon this content and introduces some new topics.

Definition of Sponsor

The draft guidance explains that there may be more than one Part 54 "sponsor" that needs to collect financial disclosure information from the investigators. As an example, it states that if a public or academic institution conducts a study without support from a commercial sponsor, but a pharmaceutical company provides the study drug for free, then both the pharmaceutical company and public/academic institution are considered sponsors for purposes of the financial disclosure regulations. Further, the $25,000 threshold for significant payments of other sorts (SPOOS) should be calculated separately for each sponsor.

Agency Actions

The draft guidance makes clear at the outset that FDA may refuse to file a marketing application that does not contain the information or certification required by the regulations. While the current guidance states that FDA does not anticipate having to use its refusal to file authority very often, the draft guidance omits this statement, which suggests that FDA will be taking a harder line when enforcing the regulations.

Submission of Financial Disclosure Information to FDA

In the draft guidance, FDA goes into greater detail than the current guidance on how to submit investigator financial disclosure information to FDA. For example, FDA proposes that applicants provide a table that indicates, for each clinical investigator, whether the applicant is making a Certification (Form FDA 3454)[3], a Disclosure Statement (Form FDA 3455)[4], or a certification that it acted with due diligence but was unable to obtain the information (option 3 on Form FDA 3454).

The draft guidance also offers a new process for making disclosures where multiple investigators have disclosable interests. The applicant can submit a single Form FDA 3455 with attachments that identify all clinical investigators and, for each investigator, identifying the study, the details of their financial arrangements, and the steps taken to minimize bias.

Due Diligence

The draft guidance significantly expands what FDA means by "due diligence." It identifies specific steps that applicants should take if the investigators' whereabouts are unknown. The draft guidance also expects sponsors to have certain financial data in their own records. Further, it notes that information about proprietary interests that investigators may have in the test product (such as patents and trademarks) is publicly available.

Timing of Data Collection and Purpose

In several places, the draft guidance states that investigational new drug (IND) application and investigational device exemption (IDE) application sponsors are required by the regulations to obtain investigator financial information prior to allowing them to participate in the study. FDA also "strongly encourages" sponsors of studies not conducted under an IND/IDE to gather this information prior to study initiation, and urges sponsors to err on the safe side by collecting the financial disclosure data from investigators up front, even if the sponsors are not certain whether the study would be covered by the regulations. The draft guidance emphasizes that this holds true equally for domestic and foreign studies.

FDA notes that proper study design is an important means of minimizing potential bias resulting from investigator financial interests. In addition to giving examples of ways to minimize bias, the draft guidance explains that by collecting the data early, the sponsors will have time to work with FDA to design the study in a way to minimize bias.

Nature of Financial Interests

The draft guidance provides additional detail about how financial information should be disclosed to FDA. However, just as the current guidance requires sponsors to make judgment calls, the draft guidance leaves some open questions. For example, it states while FDA expects that in most cases, equity interests in publicly traded mutual funds will not be reportable, they would be reportable if the fund invested a substantial proportion of its capital in the sponsor. Yet, it does not explain what "substantial proportion" means. FDA does answer an open question from the current guidance by stating that entertainment costs would be tracked as SPOOS.

Financial Disclosure Questionnaires

In the draft guidance, FDA addresses a common point of confusion for many sponsors, namely whether they can use Form FDA 3455 to obtain the financial disclosure information from their investigators. Form FDA 3455 is designed for applicants to use when reporting financial information to FDA, and does not capture the nuances of the financial disclosure regulations. Therefore, FDA advises sponsors to develop their own financial disclosure questionnaires for investigators to complete.

Time Period Covered by Regulations

The regulations require sponsors to track financial disclosure information during the course of the study and for one year following the study's completion. The draft guidance provides clarification about when the study is considered to have "started" by explaining that "during the course of the study" begins when the investigator enters into an agreement with the sponsor to conduct the study. While this is an improvement over the current guidance, sponsors will still need to decide whether to look back to when the investigator orally agreed to conduct the study (or earlier if it appears that the parties are trying to do an end run around the regulations) or when the parties signed the clinical trial agreement.

Studies

The draft guidance provides minor clarifications to the definition of "covered clinical study." Further, the draft guidance expands the current guidance's coverage of foreign studies. In the draft guidance, FDA strongly encourages applicants to arrange for collection of financial disclosure information prior to initiation of the foreign study. If the foreign study was not originally intended for submission to FDA, the applicant is expected to collect financial disclosure information retroactively by contacting the sponsor and/or investigators.

For an IND sponsor that is not sure if the study will be a covered clinical study, the draft guidance expands on the current guidance by suggesting that the prudent IND sponsor will collect information for most studies in case the studies are ultimately subject to the regulations.

The draft guidance explains that studies to support the effectiveness of a new claimed indication are covered by the regulations, but labeling comprehension studies are not.

Factors for FDA Review of Disclosed Financial Interests

In contrast to the current guidance, which does not go into detail about how FDA will evaluate the disclosed financial interests, the draft guidance states that FDA reviewers will consider factors such as:

- whether multiple investigators were used
- whether most investigators had no disclosable financial interests

- total number of investigators and subjects in the study
- number and percentage of subjects enrolled by the disclosing investigator
- information obtained from on-site inspections
- design of the clinical study (double-blind, single-blind, placebo-controlled, active controlled)
- method of randomization
- nature of primary and secondary endpoints (objective, subjective)
- method of endpoint assessment
- method of evaluation
- whether someone other than the disclosing investigator measured the endpoints
- the results of the investigator compared to the results of other investigators in the study

To analyze the risk of bias, the FDA reviewers may re-analyze the data excluding the investigator's results, compare results from more than one investigator, and/or determine if the results can be replicated over multiple studies. The reviewers will also examine the steps taken to minimize the potential bias for investigators who had disclosable financial arrangements, as those steps are described on the attachment to the Form FDA 3455.

FDA Documentation of Review

Consistent with FDA's transparency initiative, FDA explains how it will document the review of financial disclosure information, and describes some items the FDA reviewers should ensure are included in the applicant's financial disclosure. The draft guidance directs reviewers to ensure that if a financial interest is disclosed, then the disclosure should include an attachment describing the details of the disclosed interest along with the steps taken to minimize the potential for bias.

The reviewer will also address whether the disclosed financial interest raises questions about the integrity of the study data, and will describe actions taken to address these questions or will explain why no action was taken. Reviewers will ensure that sponsors who rely on the due diligence exemption provide adequate justification for why the information could not be obtained as well as efforts made to obtain the information.

FDA Soliciting Comments on FDA Public Disclosure of Investigator Financial Interests in the Sponsor

The current guidance states that FDA "expects that only rarely" would it be justified in disclosing an investigator's equity interest publicly, specifically when the public interest clearly outweighs the investigator's privacy interest. In a direct departure from the current guidance, the draft guidance recognizes the growing interest in public disclosure of financial arrangements between industry and physicians, but acknowledges that FDA needs to balance transparency with the right to privacy of clinical investigators.

FDA is considering options for disclosure such as including investigator financial disclosure information in the documentation released upon product approval for marketing. The agency is seeking comments on this issue, including whether the information released should be a summary of the investigators' financial disclosures/certifications, a listing of financial interests with the investigator's name de-identified, or a listing by clinical investigator.

Ambiguities Persist

While the draft guidance offers much-needed clarification of certain regulatory requirements as well as valuable insight into FDA's current thinking on enforcement, as with the current guidance, if the draft guidance is adopted, sponsors will still need to make judgment calls regarding whether certain financial arrangements should be disclosed to FDA, particularly with regard to SPOOS.

For an in-depth discussion of the regulations and current guidance, please see "FDA's Financial Disclosure Regulations: Careful Compliance in a Changing Landscape Part I" in the November 2010 issue of *Regulatory Focus*[5], and "FDA's Financial Disclosure Regulations: Careful Compliance in a Changing Landscape Part II" in the December 2010 issue of *Regulatory Focus*.[6]

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