



Rec 12/30/99 JB

Dockets Management Branch (HFA 305)
Food and Drug Administration
5630 Fishers Lane
Room 1 O-61
Rockville, MD 20852
Docket No. 99D-4396

December 24, 1999

Dear Sir/Madam:

Attached are comments which are being sent for your consideration regarding FDA's *Industry Financial Disclosure by Clinical Investigators, Draft Guidance* which was released on October 25, 1999. The FDA's docket number for the Part 54 guidance document is: **99D-4396**.

Note that two categories of comments are enclosed: (I) Request for Clarification of Issues Addressed in the Draft Guidance, and (II) Request for Guidance on Issues Not Addressed in the Draft Guidance.

We hope that you find this list useful in clarifying and adding to the pending Final Guidance document. Thank you for your consideration.

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I. Request for Clarification of Issues Addressed in the Draft Guidance

Comment Number	Location within Draft Guidance	Comment or proposed replacement text
1.1.	Q&A #2	<p>During the June 1999 Workshop co-sponsored by FDA and DIA, the FDA stated that either Forms 3454 and 3455, or similar forms created by Applicants could be used to report the required information.</p> <p>Please clarify if only FDA “approved” forms should be submitted by Applicants.</p>
1.2.	Q&A #3	<p>Only one example of “responsible corporate official or representative of the applicant” is listed: the CFO.</p> <p>It is recommended that “Regulatory Affairs officer” be listed as another example. If FDA believes further clarification is needed for the Guidance, they could state that it is FDA’s expectation that responsible representative’s positions will be listed in the Applicant’s corporate management-approved financial disclosure or FDA submissions process SOP(s).</p>
1.3.	Q&A # 9&13	<p>Both of these Q&As state that Applicants need not submit new financial information to FDA after the original submission. However, it is suggested that the Guidance state whether it is acceptable to the FDA for Applicants to utilize and report a “reasonable” collection deadline (eg 3-6 months) prior to the submission target date. This time lag is needed particularly for large studies, foreign sponsored and non-Applicant sponsored studies; a similar precedent has been applied to submissions regarding safety information.</p>
I.4.	Q&A #10	<p>The last paragraph of Q&A #10 indicates that ancillary staff are sometimes included on a site’s 1572. For clarity, it is recommended that two corrections be made. Recommended changes are in bold type: “. . . For purposes of this rule, the terms investigators and subinvestigators usually include persons who sign the form FDA 1572 , who are listed in item 6 of the Form FDA 1572, are identified in protocol amendments. . .”</p>
1.5.	Q&A #11	<p>The second sentence of the answer refers to the wrong section of Part 54; 54.2(c). The reference should apparently be to 54.2(e), covered clinical studies. Might also refer to Federal Register notice 63,251, 12/31/98, p. 72174.</p>

I. Request for Clarification of Issues Addressed in the Draft Guidance

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1.6.	Q&A #11	There is a typo in the 1 st sentence of the second paragraph; the text should apparently read “(see 21 CFR 312.10...”
1.7.	Q&A # 13 and 14	These Q&A’s should be clarified to state that it is the equity interests in the sponsor’s company(ies) which need to be reported. Further, as stated by the FDA representatives at the November 1, 1999 FDA/DIA workshop, the Guidance could define that equity interests in related affiliates and parent companies are excluded from the reporting requirement.

I. Request for Clarification of Issues Addressed in the Draft Guidance

Comment Number	Location within Draft Guidance	Comment or proposed replacement text
1.8.	Q&A #15	<p>This Q&A discusses reportable fluctuations in equity interests, however, the answer could be misconstrued by the reader; they may confuse the “no threshold limit” reporting requirement for “non-publically traded” interests with the >\$50,000 threshold reporting requirement for “publically traded” interests.</p> <p>It is notable that section <i>II. Financial Disclosure Requirements</i>, within <i>Disclosable Financial Arrangements</i>, items C and D of the Draft Guidance nicely defines the two subcategories of significant equity interest.</p> <p>The various conforming amendments defined in the February 1998 Final Rule require Investigators to provide “sufficient” and “accurate” information to Sponsors (pp.5252-5253), but no detailed definitions or methodologies on how this is to be achieved are provided there. However, based on comment 8 in the Final Rule (pp. 5236-5237), the FDA “believes that a \$50,000 disclosure threshold strikes the appropriate balance between the agency’s need to be aware of and help to minimize the potential for bias in clinical data and the need to avoid unreasonably burdening clinical investigators and applicants.” Elsewhere in the Rule and Draft Guidance, it is stated that financial disclosure information is but one piece of information utilized to assess the acceptability of clinical data. It is unclear to the reader how tracking nominal increments in value are of use to the FDA or Sponsor, and non-burdensome for all parties.</p> <p>It is recommended that the Answer to Question 15 be re-worded to provide that Investigators, and subsequently Applicants, need only report the first instance of publically traded equity interests in the Sponsor of \$50,000 or greater. {The threshold for potential bias has been met; other non-financial information will be needed to assess bias.} If FDA deems additional information on publicly traded equities as critical, perhaps a “sizable jump” in equity interest could then be defined in the Guidance as an additional \$10,000 (even \$50,000) increase in value of an Investigator’s equity holdings in the Sponsor.</p>

I. Request for Clarification of Issues Addressed in the Draft Guidance

Comment Number	Location within Draft Guidance	Comment or proposed replacement text
1.9.	Q&A #25	This Q&A discusses access of Investigators' financial information during the review process. It is recommended that this description also include a statement regarding access (or lack of access) by FDA investigators (DSI, etc.) during Sponsor/Applicant audits.
1.10.	Q&A #26	In t h e first sentence of the answer, the phrase "would be protected" occurs twice in a row.
1.11.	Q&A #27	<p>For clarity of the answer, it is recommended that the first sentence read: " Yes, during a Sponsor inspection..."</p> <p>Additionally, the answer could be clarified to state that an Investigator does not have financial records retention requirements, and so their availability is not required for an Investigator's site inspection, however, each investigator may choose to keep a copy of their financial certification/disclosure statements within their own personal files.</p>
1.12.	Q&A #28	Since Part 312.57 refers to "Sponsors" and Part 54.6 refers to "Applicants", and since the term "manufactures" is not defined in the Rule, it is recommended that the this question be corrected to read: " What kind of documentation is necessary for Sponsors/Applicants..."

II. Request for Guidance on Issues Not Addressed in the Draft Guidance

Comment Number	Issue Category	Comment or proposed text
11.1.	Identification/ listing of employee investigators	<p>Neither the Rule nor the Guidance currently specify whether employee investigators need to be identified or accounted for in an Application. Please provide guidance.</p> <p>Also, is it appropriate for Form 356H to refer to investigator lists (employee/non-employee) elsewhere in the Application?</p>
rl.2.	Significant Payments: applicability timeframe	<p>Section II, Financial Disclosure Requirements, section E provides guidance on Significant Payments of Other Sorts. Please clarify whether or not the guidance in that section applies <u>only</u> to studies that are ongoing on or after February 2, 1999.</p>
lr.3.	Initial time point for association of each Investigator's financial interests in the Sponsor	<p>Although Q&A #12 discusses completion of the study, it is equally important to define the initial time point for which each Investigator needs to associate financial interests in the Sponsor.</p> <p>Since some Investigators may be added to the study weeks, months, even years after the study start, it is recommended that the Guidance state that for practical purposes, the reporting time frame is Investigator specific. An Investigator's "participation start date" is the date they initiate their participation in the study (i.e. date they sign the protocol or study agreement). The Guidance could also note that Sponsors/Applicants may choose to use an earlier date (e.g. first Investigator's study initiation date) for ease of information collection and processing.</p>

II. Request for Guidance on Issues Not Addressed in the Draft Guidance

<p>11.4.</p>	<p>Site initiation after receipt of Investigator Commitment Parts 312.53 and 54.4</p>	<p>During the DIA/FDA Workshop on Nov. 1, 1999. It was noted by FDA that a site should not be permitted to enroll patients (receive study drug) until all of the investigators listed on the site's Form 1572 have provided financial disclosure statements.</p> <p>Since Sites often include non-physician staff on the 1572, and because the definition of Investigator is different in Part 312 than it is in Part 54, it is recommended that the Guidance indicate that a Site may begin protocol defined, subject-related activities only after the Principal Investigator(s), listed in Box 1 of the Form 1572, provide(s) their Financial Disclosure/Certification and Commitment. Further, the Guidance could state that use of each additional Investigator at the Site should occur only after they provide their financial information/commitment to the Sponsor.</p>
<p>11.5.</p>	<p>Clarification on "Sponsor" definition and use of data from independent research groups, including NIH</p>	<p>Frequently, independent health research groups, as well as the NIH receive "non-directed" drug supplies or funds from Pharma companies. The study results may subsequently be of interest to companies who believe that the observations support expansion of their drug's label.</p> <p>Additionally, the independent research group may not be informing investigators of the source of funds or supplies provided without stipulation by the Pharma company; therefore there is no association to the company to result in a bias.</p> <p>If the independent research groups do not collect certifications/disclosures during the study and/or do not have systems to track addresses of investigators, Pharma companies need to know whether they should withdraw support from these groups if they refuse to comply with the regulation fully. Further, will they have the ability to submit the data even if the independent research group did not comply with the regulation?</p> <p>It is recommended that Guidance specify that when Pharma companies do not take part in study design or Investigator selection, that they are not to be considered a study Sponsor.</p>

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