



## It's the Law

# Compliance with FDA's Financial Disclosure Rule

by David Clissold, Esq.

Last year, the Food and Drug Administration (FDA) published its final rule on Financial Disclosure by Clinical Investigators.<sup>1</sup> FDA subsequently revised these requirements in response to a citizen's petition.<sup>2</sup> In the August 1999 issue of *Regulatory Affairs Focus*, Heather Lamberg provided a superb summary of FDA's new financial disclosure regulation. The purpose of this article is to describe some of the uncertainties companies face in attempting to comply with this unprecedented regulatory requirement.

### When is a Study Complete?

The regulations require applicants to certify to the absence of, or disclose, certain financial arrangements "during the time the clinical investigator is carrying out the study and for one year following completion of the study."<sup>3</sup> In the preamble to the final rule, FDA explained that a study is complete "after enrollment of all the subjects and follow-up [of] subjects in accordance with the clinical protocol...."<sup>4</sup> FDA also explained that the purpose of this clarification was "to further reduce the possibility that clinical investigators could exert undue influence during final data analysis."<sup>5</sup>

The phrase "follow-up of subjects," however, is subject to multiple interpretations. It could mean the last actual patient visit, the last communication with a patient, the last case report form entry or the date on which the final "data query" is resolved.<sup>6</sup> Alternatively, a "bright-line" test of when a study is complete is the date of "database lock." Depending on which date FDA accepts, this would mean that the period defined in the regulation as "one year following completion of the study" is also subject to multiple interpretations. The longer that period of time, the greater are the administrative burdens on FDA, the sponsor, the applicant and the investigator. Applicants should be able to adopt any reasonable definition of "completion of the study" that comports with the rule, and FDA should be prepared to accept multiple definitions of that phrase.

May an applicant submit a complete, reviewable application if the relevant data and appropriate financial disclosure information are submitted to the agency before the expiration of the one-year post-study period?

The regulations require applicants to certify to the absence of, or disclose, certain financial arrangements

"during the time the clinical investigator is carrying out the study and for one year following completion of the study."<sup>7</sup> However, FDA argued that the purpose of the financial disclosure rule is "to ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the sponsor of any drug, biological product or device marketing application."<sup>8</sup> Therefore, at least at the point that the data is submitted to FDA, any clinical investigator's possible bias is moot, since the investigator's ability to affect the data submitted to FDA is eliminated. FDA apparently recognized this point, stating that the agency needs to be "aware of payments and financial arrangements by sponsors of covered studies that could lead to the introduction of bias into the clinical trial process...."<sup>9</sup> In the preamble to the proposed rule, FDA also recognized that the investigator's ability to affect the reliability of data, through bias or otherwise, is limited to the time that an investigator actually has control over the data. "In any discussion of potential sources of bias, it is important to distinguish between the actual conduct of studies and collection of data by clinical investigators, on the one hand, and the use of those studies, i.e., the analysis, interpretation and presentation of the data from those studies by the sponsor, on the other."<sup>10</sup>

In the proposed rule, the definitions of "significant equity interest" and "significant payments of other sorts" did not include the one-year post-study requirement. In light of the purpose of the rule, it is not clear what additional assurance FDA gains from forcing applicants to comply with the one-year post-study requirement. The effect of this requirement is especially egregious if the relevant data is ready for submission to FDA before the expiration of the one-year period. Under a literal reading of the current rule, such an application would apparently be *unreviewable* since the applicant could not certify to the absence of significant equity interest or significant payments of other sorts for the time period specified in the regulation.<sup>11</sup> In such a case, the applicant's only apparent option is to wait for the one-year post-study time to expire.<sup>12</sup> This can not be the intended result since it would significantly delay the marketing of beneficial products. FDA should clarify whether an application could be submitted before the end of the one-year post-study period.

Why doesn't the rule apply to "large, multicenter studies" of efficacy as well as safety?

In the petition for reconsideration of the financial disclosure rule, the petitioner requested that "studies, which are large and involve multiple investigative sites," should be excluded from the rule because in such a case, the ability of any single investigator to influence the data would be too limited to justify the burdens and costs for the sponsors and FDA.<sup>13</sup> In its action on the petition for reconsideration, FDA apparently agreed with the petitioner and acknowledged that "because these studies generally have large numbers of investigators, no single investigator has a major responsibility for the data."<sup>14</sup> FDA then amended the definition of "covered clinical study" to include certain language from the preamble to the final rule that was inadvertently omitted from the codified language of the February 2, 1998, final rule. With respect to multicenter trials, the rule now apparently excludes only "large open safety studies conducted at multiple sites."<sup>15</sup>

However, "studies with large numbers of investigators" may be open or randomized. Moreover, both safety and efficacy studies can involve multiple sites. In these large trials, no single investigator would have a major responsibility for the data regardless of whether the endpoint is safety or efficacy, and regardless of whether the study design is open or randomized. The existence of multiple investigators obviates the need for the information required by the regulation irrespective of whether the study is gathering safety and/or efficacy data. FDA should explain the reason that safety studies were distinguished from efficacy studies, and explain why multicenter efficacy trials need to be subject to the burdens of this rule.

May an applicant rely on the investigators' compliance with their duty to update information, or must the applicant send multiple inquiries to each investigator?

Clinical investigators have a specific duty to update their financial disclosures if there are relevant changes in the information originally disclosed.<sup>16</sup> The sponsor, in turn has an obligation to obtain "a commitment from the clinical investigator to promptly update this information."<sup>17</sup> If the sponsor obtains a written commitment from the clinical investigator to update promptly the information, then the sponsor should be able to rely on the clinical investigators to update their response if there are changes. If the sponsor is required to send out repetitive requests for updated information from each clinical investigator in order to make the appropriate certification or disclosure, the paper work that needs to be tracked and reviewed by

the sponsor for each clinical investigator increases dramatically. FDA should allow sponsors to rely on the investigators' obligation to keep the sponsor informed.

## Conclusion

FDA should publish a guidance document that clarifies the issues raised by the financial disclosure rule. Companies need to be aware that compliance with the rule is not merely a matter of completing the appropriate form. FDA also should be flexible in its interpretation of compliance, especially in light of the new administrative burdens this rule places on all parties. As sponsors, applicants and investigators gain experience with this rule, different interpretations as to the methods by which regulated entities may comply with the requirements are emerging. The shared feature is that all methods of compliance are more expensive and burdensome than FDA anticipated.

## Notes:

- 1 63 *Federal Register* 5233 (February 2, 1998).
- 2 63 *Federal Register* 72171 (December 31, 1998).
- 3 21 C.F.R. §§ 54.2(b) and (f).
- 4 63 *Federal Register* at 5242. Presumably the omission of the word "of" was merely inadvertent.
- 5 *Id.*
- 6 Typically, after the last follow-up of subjects, at least some of the data in the clinical database must be validated. In part, this validation may be accomplished by issuing "data queries" to the sites, through which incomplete or contradictory information may be resolved. This resolution often requires the input of the investigator.
- 7 21 C.F.R. §§ 54.2(b) and (f) (emphasis added).
- 8 63 *Federal Register* at 5233.
- 9 *Id.* at 5235 (emphasis added).
- 10 59 *Federal Register* 48708, 48709 (September 22, 1994).
- 11 See 21 C.F.R. § 54.4(c).
- 12 Nor should the applicant be required to file an amendment to include the one-year, post-study financial disclosure information. Because the investigator's ability to influence the data in such a case is eliminated before the data are submitted to FDA, such an amendment would serve no purpose while only increasing the administrative burden on applicants.
- 13 FDA Docket No. 93N-0445; Petition for Reconsideration at 6 (July 31, 1998).
- 14 63 *Federal Register* at 72174.
- 15 21 C.F.R. § 54.2(e) (emphasis added).
- 16 See, e.g., *Id.* § 312.64(d).
- 17 See, e.g., *Id.* § 312.53(c)(4).

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