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PhRMA

September 24, 2001



Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852



RE: FDA Request for Comments on Proposed Collection of Information Concerning Financial Disclosure by Clinical Investigators; Docket No. 01N-0308, 66 *Fed. Reg.* 38712 (July 25, 2001)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing approximately $ 30 billion this year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures. PhRMA is pleased to provide these comments in response to the FDA's request for comments on the proposed collection of information concerning the disclosure of financial information by clinical investigators to sponsors, and by applicants to the FDA.

In response to the FDA's request for comments, PhRMA provides the following information in response to FDA's four specific questions:

1. *Whether the proposed collection of information is necessary for the proper performance of the FDA's functions, including whether the information will have practical utility;*

The FDA's collection of information that is the subject of this request for comment imposes data collection, reporting, and retention burdens on clinical investigators, sponsors, and applicants to the FDA that provides no benefit to any of the participants in the effort. In a recent PhRMA survey, member companies reported that, for all of 2000, less than 1% of all investigators, subinvestigators, and their spouses and dependent children reported any financial relationship with the sponsor to disclose. In other words, everyone involved in the system is spending time and energy so that FDA can learn that there are virtually no financial relationships between sponsors and investigators that might bias clinical study results.

The "less than 1 percent" reported above is based largely on responses from U.S. investigators. The response from non-U.S. studies is very limited. This seriously affects global companies who conduct substantial numbers of studies outside the United States.

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With respect to proprietary interest and variable compensation, the FDA data requirements result in reporting primarily by start-up companies who have limited resources and use these payment methods as techniques to fund their clinical trial programs. The large global companies almost never utilize these two forms of compensation. Given the small number of financial relationships that are reported (< 1 %), PhRMA would like to hear from the FDA whether their collection of this information has generated any useful information with respect to the quality or integrity of clinical trial data.

2. *The accuracy of the FDA's estimate of the burden of the proposed collection of information, including the validity and methodology and assumptions used;*

PhRMA member companies report that it takes approximately fifteen (15) work weeks to collect, compile, and verify the information about the financial relationships with investigators and subinvestigators for a single Phase III study involving 50 sites. The individual company responses ranged from a low of approximately 110 work hours to a high of almost 900 work hours, with the majority of companies reporting higher, rather than lower numbers of work hours. These figures translate into a low of approximately three and a high of approximately 26 work weeks. Studies of such size are common in Phase III studies; some New Drug Applications include more than one multi-site Phase III studies. It is reasonable to conclude that a somewhat smaller amount of staff time is necessary to collect, compile, and verify information for Phase II and Phase I studies, but some time is required. Therefore, PhRMA concludes that the FDA's estimate of one or four hours to complete a response is entirely unrealistic.

Source of Information – PhRMA companies typically rely on investigators and subinvestigators to report some information and compile from company internal sources other information about the financial relationship between the sponsor and the investigators. Many companies report that they have purchased or paid for the development of computer software (or modifications to existing software) to compile information that may be available elsewhere within the companies. This is done to track some of the clinical investigators' financial information that FDA requires applicants to submit, such as proprietary rights and significant payments of other sorts (SPOOS) to investigators or subinvestigators. Development costs for this software are considerable, well beyond the FDA's estimate of reporting costs of less than $ 450,000 annually. Once developed, the software requires some investment to maintain. Some companies have established new staff positions and/or new departments to handle the collection, compilation, verification, reporting and retention of clinical investigator financial disclosure. Indeed, without the software investment, companies would need more staff to manage the information collection systems.

PhRMA urges the FDA to reconsider its estimates of the reporting burden posed by this rule, and submit to the Office of Management and Budget (OMB) a more realistic estimate of the required reporting time.

3. *Ways to enhance the quality, utility, and clarity of the information to be collected;*

Covered Clinical Studies – PhRMA member companies report some difficulties in determining what studies are covered clinical trials, and variations across reviewers in what studies are indeed "covered studies" under the FDA guidance. Thus, some companies collect, compile and report to FDA investigator financial information from all studies, regardless of whether they are "covered studies." Some companies have collected information for only those studies they understood were covered by the guidance, and then had to go back to investigators and subinvestigators, well after completion of the studies and submission of the application to the FDA, to collect financial information. PhRMA recommends that the FDA clarify the definition of covered study and ensure that reviewers apply a consistent definition of what studies are actually covered by the clinical investigator financial reporting requirement. In addition, PhRMA repeats its recommendation that the FDA exclude all large, multi-center studies in which no single investigator contributes less that 20 percent of the data.

Locating Investigators and Subinvestigators – Companies also report that they have considerable difficulty locating investigators and subinvestigators who have left the study, or the clinical trial site, prior to completion of the study or completion of the one-year follow-up period. FDA inspectors have faulted companies for not having records of financial information for all subinvestigators who participated in a study for a portion of the study, even when the companies' records contained a notation that it was not possible to locate the individuals for the one-year-post-completion data collection. This has occurred even though the FDA has said, in the Guidance, that the sponsor is responsible for determining what constitutes "due diligence" in attempting to locate investigators and subinvestigators.

PhRMA recommends that the FDA ensure that inspectors, as well as reviewers, understand what constitutes due diligence in attempting to locate investigators and subinvestigators who have left the clinical trial or the clinical trial site and what records provide adequate evidence that the company has exercised due diligence. PhRMA also urges that the FDA consider establishing a definition of what constitutes "due diligence" in attempting to locate investigators and subinvestigators who have left a clinical trial before its completion or at one year after trial completion. In addition, as noted below, PhRMA recommends that the FDA limit the number of people required to provide financial information to the study sponsor.

Definition of Investigator and Subinvestigator – Many PhRMA companies use a broad, rather than a narrow, definition of who at a clinical trial site might be considered an investigator or subinvestigator. This is done to avoid an FDA reviewer requiring the

company to attempt, after-the-fact, to collect financial relationship information from people who become more difficult to locate with the passage of time.

Companies report that residents, interns, nurses, coordinators and others find it amusing that the government believes that they might be able to bias clinical trial data based on their financial relationship with the sponsoring company. The FDA rule should be clear enough that everyone would reach the same conclusion about who is and who is not required to submit financial information to the sponsor. For example, if the FDA applied the financial disclosure rule to the principal investigator and his or her dependents, everyone would know who should provide the information; many people would be spared the necessity of completing unnecessary paperwork; sponsors would be spared the expense of compiling, verifying, reporting and storing unnecessary information; and the FDA would be spared the review of unnecessary information.

Some investigators participating in multiple clinical trials object to compiling and reporting the same information for multiple sponsors, or at different times for the same sponsor for different studies. This problem is exacerbated by the requirement that investigators and subinvestigators report information about potential financial relationships with sponsors.

PhRMA recommends that the FDA clarify and further limit the definition of investigator and subinvestigator, so that companies do not need to collect information from such a large group of people at each clinical trial site, and so that everyone would reach the same conclusion, for an individual trial, about who is and is not required to submit financial information to the sponsor. For example, data collection could be limited to the person who signs the FDA Form 1572.

4. *Ways to minimize the burden of the collection of information on the respondents, including through the use of automated collection techniques when appropriate, and other forms of information technology.*

Individual PhRMA members have developed mechanisms to collect, compile, verify, and maintain the records of clinical investigator financial relationships with sponsors of covered clinical trials. See the response to number 1, above. The problem is not the initial cost of development of the mechanisms (although this may be high), but the on-going costs of collecting, compiling, verifying and maintaining the information when the information does not add anything additional for the sponsor, applicant, or FDA. The FDA Guidance states that a sponsor may rely upon information gathered from the investigators, with minimal effort from the sponsor. Yet the FDA makes the sponsor responsible for the quality of the financial data collected from investigators and subinvestigators. It is also the sponsor, or the applicant, who will be subject to the FDA's criticism if an investigator fails to report information that the FDA requires be reported. Consequently, responsible companies have created departments and invested considerable sums to create data systems to ensure

compliance with the rule and Guidance. PhRMA repeats its recommendation that the FDA limit the scope of people for whom sponsors are required to collect, compile, and report financial relationship information.

In light of the very small number of investigators who disclose any reportable financial relationship with study sponsors, the FDA should reconsider some of the dollar amounts above which investigators and others are required to report financial information, such as the total dollar amount for significant payments of other sorts and a significant change in an investigator's financial holdings in a sponsor.

Other recommendations that would streamline the data collection process include:

- Allowing sponsors to use email to communicate with potential investigators about the financial disclosure requirements prior to initiating a covered clinical trial and with investigators during covered clinical trials. This would include sending disclosure forms and reminders to investigators by email.

- Allowing investigators to fax completed forms to the sponsor, rather than requiring that sponsors retain forms with original signatures.

- Allowing sponsors to collect financial disclosure information at or near the start of each investigator's participation in the clinical trial, rather than prior to participation.

We would be pleased to provide additional information or answer any questions that you might have.

Sincerely,

Marjorie E. Powell