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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 10-61
Rockville, Maryland 20852

RE: [Docket No. 99D-4396]
DRAFT Guidance for Industry: Financial Disclosure by Clinical Investigators

To whom it may concern:

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy – to discover new medicines through breakthrough research – encourages us to spend more that $ 2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Research, by its nature, is a multidisciplinary and highly risk-intensive business. It depends upon many variables, including: prolific source materials, first class talent, adequate funding, efficient and effective quality processes and procedures, and a predictable regulatory environment.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at one time through comprehensive R & D programs.

Merck's research scientists ensure that our research process continues to identify medically important product candidates from thousands of chemicals and molecular entities screened each year. Only one in ten of these research product candidates is selected to enter the Development testing programs. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

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Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

In the course of bringing our product candidates through developmental testing and clinical studies, Merck scientists regularly involve hundreds of physicians that are affected by this proposal while testing our potential products in clinical research trial participants. Through discussions with these individuals and through internal reviews of the steps necessary to secure the obligatory information, we are very interested and well qualified to comment on this FDA draft Guidance for Industry: ***Financial Disclosure by Clinical Investigators.***

Merck commends the U.S. FDA for recognizing the inherent issues surrounding the final regulation ***Financial Disclosure by Clinical Investigators*** and by addressing and clarifying many of the points outlined in the original regulation published February 02, 1998 and amended on December 3 1, 1998. Sensible and clear guidance is the only avenue to providing sufficiently complete, accurate and meaningful information regarding ***potential*** financial bias in the conduct of clinical investigations.

Highlighted below are our specific comments to the Question and Answer format of the draft Guidance and a proposed wording for the response ("A") that we believe more completely or appropriately addresses the question.

Specific Comments:

Part IV. Questions and Answers

2. Are applicants required to use FDA forms 3454 and 3455 in reporting this information?

Comment: The answer appropriately details requirements for completing Forms 3454 and 3455, but should also indicate where the information should be included regarding investigators for whom incomplete information is known (i.e., required information known with the exception of one or more disclosable arrangement(s)). For example, for an ongoing clinical trial, the investigator may NOT return the form requesting financial disclosure information, however, the sponsor may know that (1) no financial arrangements have been made for a positive outcome and (2) through internal searches of financial databases, that no "payments of other sorts" exceeding $25,000 have been made, In this example, the sponsor/applicant could ***certify*** the investigator for two of the four requirements, but could not provide full information. In evaluating the ***potential*** for bias through the review of financial disclosure information, the Agency should have such specific details in order to make the most accurate assessment.

Recommendation:

A. Yes. The regulations require that the applicant submit a completed Form 3454 for all investigators certifying to the absence of all financial interests and arrangements. For any clinical investigator for whom the applicant can only provide partial certification due to incomplete information, a list or table should be appended to Form 3454 to include such details. For all investigators that have known disclosable information, the applicant must submit a completed Form 3455 disclosing the financial interests and arrangements and steps taken to minimize bias.

9. Should financial information be collected prior to study start?

Comment: While, in theory, it would be best to know all financial information regarding all clinical investigators ***prior*** to participation in a trial, the Agency cannot expect that sponsors will necessarily have access to all the required elements before the initiation of a study. In reality, attempts can be/should be made to obtain such information, however, non-receipt of the requested information should not mandate that: (1) such investigator(s) not be used or (2) discussions between the Agency and the sponsor should ensue. More practically, for multicenter, double-blind, randomized trials, sufficient control of bias should exist ***by study design*** to eliminate the absolute necessity to receive financial information from investigators prior to study initiation.

Recommendation:

A. Yes. 21 CFR 312.53 and 21 CFR 812.43 state that before permitting an investigator to begin participation in an investigation, the sponsor shall obtain sufficient accurate financial information to allow the sponsor to submit complete and accurate verification or disclosure statements required under Part 54, and to commit to promptly update this information if any relevant changes occur during the course of the investigation and until all data discrepancies have been addressed and the database has been locked (SEE RECOMMENDATION 13 BELOW). The Agency recognizes that, although such information will be requested by the sponsor prior to study initiation, there are circumstances when such information may not be forthcoming. Depending on study design and the pre-specified controls for bias, it may be appropriate to utilize certain investigators when all financial interests are not know prior to study start. In situations where such controls do not exist and financial interests are not fully known, the sponsor is encouraged to consult with the Agency regarding appropriate steps to take to minimize the potential for bias.

10. What does FDA mean by definition of clinical investigator and subinvestigator? Is it necessary to collect financial information on spouses and dependent children of subinvestigators?

Comment: The Agency should use this opportunity to uniformly define, relative to other regulations/guidelines concerning clinical trials, their definition of "subinvestigator." Expectations in completing the Form FDA 1572 in this regard have clearly varied between Agency reviewers and field investigation staff as well as between individual sponsors. Merck & Co., Inc. concurs that subinvestigators listed in item 6 of the aforementioned form should meet the definition outlined in the Financial Disclosure by Clinical Investigators regulation, namely those individuals who are responsible for the treatment and evaluation of research subjects. In this regard, it should be stated that such a definition does ***not*** include study coordinators, study nurses and other study staff although they may have consistent and repetitive responsibilities for "treating and evaluating research subjects." This clarification of the term "subinvestigator" should be consistently applied throughout all FDA regulations and guidances.

Recommendation:

A. For drug and biological products, clinical investigator means the individual(s) who actually conduct(s) and take(s) responsibilities for an investigation, i.e., under whose immediate direction the drug or biological product is administered or dispensed to a subject and who is directly involved in the evaluation of research subjects. Where an investigation is conducted by a team of individuals, the investigator is the leader of the team. For purposes of this rule, the terms investigators and subinvestigators include persons who: sign the Form FDA 1.572, who are listed in item 6 of the Form FDA 1572, are identified in protocol amendments under an IND or are identified in the NDA/BLA as an investigator. Study coordinators, study nurses and other study staff who have consistent and repetitive responsibilities for treating and evaluating research subjects, however, are not included. For studies not conducted under an IND, the Sponsor and the clinical investigator will need to identify all individuals whom they consider covered by the rule in Form 3454 and/or 3455. (Remainder of response identical to draft guidance)

11. Do the reporting requirements apply to efficacy studies that include large numbers of investigators and multiple sites? Will the agency consider a waiver mechanism to exempt applicants from collecting information from clinical investigators conducting these kinds of studies?

Comment. While the Agency has clearly stated their position regarding financial disclosure requirements for multicenter clinical trials, special consideration should be given to megatrials which enroll greater than 1000 patients, particularly when such trials were initiated prior to the Regulation's effective date of February 2, 1999. Such clinical trials typically involve large number of investigators and subinvestigators; requiring retrospective financial disclosure information for/from hundreds of

investigators/subinvestigators for studies which started before this date presents a less than valuable exercise, particularly when, by sheer volume of investigators and by study design, the possibility of any bias is inherently minimized.

Recommendation

A. Large multicenter efficacy studies with greater than 1000 research subjects and with many investigators are considered covered clinical studies within the meaning of the final rule. See 21 CFR 54.2(c). However, the Agency recognizes that the retrospective collection and reporting of financial interest information from such trials that were initiated prior to the Regulation's effective date of February 2, 1999, puts a significant burden on sponsors when there is minimal opportunity for bias to affect the outcome of the trial. As such, it is the Agency's expectation, that for such large efficacy trials (>1000 research subjects), financial disclosure obligations will apply only to such studies started after the Regulation's effective date.

13. Do applicant companies need to collect information for a year after completion of the study? Who is responsible for collecting/providing this information?

Comment: It is understood that the Agency needs to assess the potential for bias in the outcome of covered clinical trials and that the "one year following completion of the study" was included in the Regulation to ensure that bias could not/did not affect the clean-up and data review process. As such, the more appropriate period for reporting financial interest information should be from study start through the "locking" of the clinical database, as all inquiries regarding the data and responses from investigators would be complete by that time. Additionally, by setting this expectation, all financial disclosure queries and searches can be completed and reported as "final" in the application.

Recommendation:

A. According to the February 2, 1999 final rule, the investigator must provide updated information when the investigator holds any equity interest in a privately held company or when stock holdings in a publicly held company exceed $50,000 in value for one year following completion of the study. In addition, sponsors/applicants must keep records on file when significant payments of other sorts are paid by the sponsor of the covered study to the investigator or the investigator's institution to support activities of the investigator that have cumulative monetary value of more than $25,000, exclusive of the costs of conducting the covered clinical studies during the study and for one year following completion of the study. FDA specified the one-year time frame because additional bias might be introduced by investigator(s) during the data review and resolution process. If this data review and resolution process is completed in less than one year following completion of the trial, then the extended time frame should include only those financial

interests through the date of the final closure or locking of the clinical database. Any updated information from investigators should be kept in sponsor's files.

20. In the case where a subsidiary company of a larger parent company is conducting a covered clinical trial, is the applicant (subsidiary company) reauired to collect information from clinical investigators about financial interests in only the subsidiary company, or is the applicant also reauired to report financial holdings, if any, of the investigator in the larger parent company?

Comment: In the response provided in the DRAFT Guidance for Industry, the Agency indicated that "if there are multiple companies providing material support for a covered study, financial arrangements must be reported in all companies providing that support since those companies will meet the definition of sponsor of the covered study." Merck & Co., Inc. argues that for such studies involving multiple "sponsors," only information in the sponsor/applicant should be provided with the given application. Payments to investigators as consultants or as honoraria should be regarded as confidential information and not be provided to other co-sponsors of the trial.

Recommendation:

A. Financial arrangements and interests of clinical investigators must be traced to the sponsor or applicant, if the applicant is acting as the sponsor of the covered clinical study. If there are multiple companies providing material support for a covered study, such joint responsibility should be clearly outlined in the application. When the multiple companies intend to submit the results from such a trial independently to the Agency, the applicant should provide only the financial interests in relationship to the individual sponsor/applicant. (Remainder of response identical to draft guidance)

23. How do significant payments of other sorts relate to the variety of payments the sponsor might make to an individual or institution for various activities?

Comment: Merck & Co., Inc. suggests that the Agency take the opportunity to identify specifically in this section what it considers "substantial payments" and recommends that no individual payment of <$1000 be included in the tabulation. Additionally, the Agency should clarify that travel arrangements, lodging and meals paid in direct association with a consultant's obligation should not be included under "payments of other sorts."

Recommendation:

A. The term "significant payments of other sorts" was intended to capture substantial payments or other support provided to an investigator that could create a sense of obligation to the sponsor. The FDA considered any individual payments of >$1000 to be substantial.

These payments do not include payments for the conduct of the clinical trial of the drug under consideration or clinical trials of other drugs under a contractual arrangement, but do include other payments made directly to the investigator or to an institution for direct support of the investigator. These payments would include honoraria, consulting fees (excluding all travel-related expenses directly associated with the consulting arrangement), grant support for laboratory activities and equipment or actual equipment for the laboratory/clinic. This means that if an investigator were given equipment or money to purchase equipment for use in the laboratory/clinic, but not in relation to the conduct of the clinical trial, the payment would be considered a significant payment of other sorts and should be reported. If, however, the investigator were provided with computer software or money to buy the software needed for use in the clinical trial, that would not need to be reported.

Finally, payments made to the institution or to other nonstudy participating investigators that are not made on behalf of the investigator do not need to be reported.

28. What kind of documentation is necessary for manufacturers to keep in case Questions about certification and/or disclosure arise.

Comment: Merck & Co., Inc. suggests that the Agency consider situations where "check stubs, canceled checks, records of direct electronic financial transactions" may be actually retained at distant locations/offices worldwide. Under such situations, it would not be practical or appropriate to collect such documentation in one location. Flexibility should be provided for individual searches of such multiple financial systems with the results being collected, tabulated and retained as sufficient documentation of such payments. Additionally, the Agency should consider the paperwork burden of keeping duplicate hardcopies of all letters sent to individual investigators requesting the required financial information.

Recommendation:

A. In addition to the applicant's Standard Operating Procedures for the request of required financial information from investigators, the applicant should retain complete records showing any financial interest or arrangement as described in the financial disclosure final rule(s) entered into between the applicant or sponsor of the covered study and the clinical investigator. In addition to an example of the correspondence and copies of information provided by each investigator regarding his/her personal equity holding and those of his/her families, applicants should retain appropriate tabulations regarding the payments the applicant has made to investigators. When archival of specific documents (e.g., check stubs, canceled checks) is not feasible, identification of the payments and its purpose and location is acceptable. (Remainder of response identical to draft guidance)

SUMMARY

The draft Guidance for Industry – ***Financial Disclosure by Clinical Investigators*** provides an excellent summary of FDA's expectations regarding the final rule. Merck & Co., Inc. appreciates the opportunity to provide comments which, from our perspective, will clarify some of the outstanding issues. We would welcome the opportunity to meet with you to discuss our recommendations.

Sincerely,

Bonnie J. Goldmann, MD

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