Docket No. FDA-1999-D-0742

COMMENTS

of

THE WASHINGTON LEGAL FOUNDATION

to the

FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH & HUMAN SERVICES

Concerning

REQUEST FOR COMMENTS REGARDING FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

IN RESPONSE TO THE PUBLIC NOTICE PUBLISHED AT
76 FED. REG. 30175 (May 24, 2011)

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5360 Fishers Lane
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Rockville, MD 20852

Re: FDA Docket No. 1999-D-0742, Draft Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators (May 24, 2011)

Dear Sir or Madam:

The Washington Legal Foundation (WLF) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) in connection with the Draft Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators (the "Guidance"), released in May of 2011. WLF addresses a few concerns with the new Guidance, including FDA's interpretation of "due diligence," and the lack of concrete guidance to sponsors and investigators as to the nature of "serious question(s) about the integrity of the data." Additionally, WLF commends FDA for rejecting the recommendation of the Office of the Inspector General (OIG) that financial disclosure be required before the pretrial application process begins. Finally, WLF submits input on the request for comments relating to public disclosure of financial information and strongly urges FDA to err on the side of privacy while appropriately informing the public of conflicts of interest.

I. Interests of the Washington Legal Foundation

WLF is a national, nonprofit public interest law and policy center based in Washington, D.C., with supporters in all 50 states. While WLF engages in litigation and participates in administrative proceedings in a variety of areas, a substantial portion of its resources are used in promoting legal policies that are consistent with a free-market economy and in defending the rights of individuals and businesses to go about their affairs without excessive intervention from government regulators.

Additionally, WLF has routinely participated in FDA administrative proceedings. *See, e.g.*, FDA Docket No. 2011-F-0172 (June 13, 2011) (response to FDA request for comments relating to Nutrition Labeling of Standard Menu Items in Restaurants and Similar Retail Food Establishments); FDA Docket No. 2008-D-0053 (April 21, 2008) (response to FDA's draft guidance for industry on good reprint practices); FDA Citizen Petition No. 2006P-0319/CPI (August 11, 2006) (documenting repeated First Amendment violations by FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) and calling on DDMAC to conform to constitutional constraints on its activities); FDA Docket No. 02N 0209 (October 28, 2002) (response to FDA's request for public comments on First Amendment issues).

I. FDA's Expanded Definition of "Due Diligence" is Unduly Burdensome and Rote in Application

FDA requires applicants to completely and accurately disclose or certify information on the financial arrangements of clinical investigators. 21 CFR § 54.4. When the applicant is unable to obtain that information, they must certify that they acted with due diligence. ("Where the applicant acts with due diligence to obtain the information required in this section but is unable to do so, the applicant shall certify that despite the applicant's due diligence in attempting to obtain the information, the applicant was unable to obtain the information and shall include the reason.") Under the 2001 Guidance to Industry om Financial Disclosure by Clinical Investigators, FDA answered the question "[w]hat does FDA mean by the term "due diligence"?" by explaining that the term "is a measure of activity expected from a reasonable and prudent person under a particular circumstance," and that applicants should "use reasonable judgment in deciding how much effort needs to be expended to collect this information." (2001 Guidance Q. 3). FDA's description was adequate at the time and should not be changed, as the new Guidance proposes, to reflect "recommendations" that are more likely to be viewed as requirements.

Indeed, one of the key principles of due diligence as a legal term is that it is a flexible term of art that depends on circumstances that would face a reasonable person in a specific situation. Merriam-Webster's dictionary provides a simple definition of the phrase: "the care that a reasonable person exercises to avoid harm to other persons or their property." *Merriam-Webster's Dictionary*, Merriam-Webster, Inc. 25 Jul. 2011. <http://www.merriam-

webster.com/dictionary/due%20diligence/>. Merriam-Webster's Dictionary of Law further defines the phrase as "such diligence as a reasonable person under the same circumstances would use." *Merriam-Webster's Dictionary of Law*. Merriam-Webster, Inc. 25 Jul. 2011. <Dictionary.com http://dictionary.reference.com/browse/due diligence>. While reasonable people can disagree as to what a reasonable person might do in a certain situation, the term "reasonable person" is well-developed in the law and provides more than enough guidance to FDA and to industry without being unduly burdensome.

It is puzzling, then, that FDA has chosen to "recommend" to sponsors and applicants a detailed routine of phone calls, letters, written memoranda, contacts with other institutions, professional associations, and even Google searches. While a "reasonable attempt" should certainly be undertaken by applicants – who should make "appropriate efforts to obtain" financial arrangement information – detailing the steps that an applicant should take can confuse those with responsibility for collecting this information. Are these merely suggestions or are they more firm than that? Is a recommendation a benchmark that the applicant must meet in most situations or is it simply a listing of steps that FDA believes a reasonable person might take?

When applicants face different situations relating to clinical investigators who cannot be found or whose financial information cannot be collected, it is necessary for those in charge of finding that information to use appropriate caution as the situation calls for. When using terms of art, such as "due diligence," FDA should leave it relatively flexible. Should an applicant who determines that an investigator has, for example, died be required to go an extra step further and

seek multiple verification of that death through the list of "recommend[ed]" steps, or simply move on and certify that they performed due diligence? By both recommending steps that applicants should take to perform due diligence and adopting the ordinary definition of that term at the beginning of the answer to Question B.6 ("a measure of activity expected from a reasonable and prudent person under a particular circumstance"), the Guidance makes the mistake of abandoning an appropriate and flexible term in favor of specific recommendations that are treated more as requirements than as guidance. While in other contexts industry undoubtedly prefers very specific standards by FDA in order to create certainty in business planning, the dilution of a well-understood term with arbitrary recommendations on steps to take only further complicates what should be a common-sense application of the rule.

II. Vague and Ambiguous Guidance on FDA Review of Financial Information Leads to Uncertainty in Industry and Reluctance of Investigators to Participate in Clinical Trials

While it is necessary for FDA to have some flexibility in reviewing financial information submitted in a marketing application – not all financial interests are created alike – it is unfortunate that there is no greater guidance to industry than a list of the types of interests that must be disclosed and a listing of the "many factors" that FDA "may consider…in making its evaluation." (2011 Guidance Q. H.3). As the Guidance acknowledges, the usual financial interest that is reported is an equity interest or a SPOOS (significant payments of other sorts). Simply stating that the amount and nature of the financial interest disclosed "may be considered" creates uncertainty in regulated firms because there is no guidance as to what the agency will

consider to be a high enough amount or an unusual enough nature to warrant serious questions about the integrity of data. Without this certainty in regulatory standards for approving a marketing application, sponsors risk loss of millions or hundreds of millions of dollars invested in completing a study, if FDA later rejects the study because an FDA reviewer determines that the study's data lacks integrity. Why should a sponsor invest such money into a study if there is an uncertain chance that a reviewer will consider some disclosed interest to warrant an agency action (including ultimate rejection of the application)? More likely than abandoning such a project, the real danger is that the sponsor will, out of an abundance of caution, use less than the most qualified of researchers so that potential conflicts of the best will not sink the project's future when reviewed by FDA.

Additionally, clinical investigators may be reluctant to participate in clinical trials if their work will be questioned – their integrity as a professional and physician – simply because they might own stock in a pharmaceutical company that could benefit from the results of their work as an investigator. Often times, the best potential investigators are those who have significant interests in potential sponsors. After all, industry and universities generally do not give SPOOS to people who do not deserve them. If a firm is concerned that these premier physicians, to whom they may have already given money for other projects or with whom they have some connection in another circumstance, might compromise the viability of the endeavor of a clinical trial, it is possible that less-than-capable investigators may be selected or that a sponsor may choose not to proceed with a trial. The cost both to the firm and to the country through a loss of good, scientific work arising from fear of regulatory uncertainty is incalculable. While 21 CFR §

54.5 and the Guidance give some indication of the types of things sponsors can do to minimize bias, they provide insufficient guidance, leaving too much leeway to reviewers with no certain standard for clinical trials to meet. For instance, Part III.B of the proposed Guidance states that equity interests of greater than $50,000 in a sponsor must be disclosed, as must significant payments of other sorts (SPOOS) in excess of $25,000 or more. While these numbers appear to be arbitrary, they have been the standard for many years under the CFR. What is unknown, however, is the nature or amount of a financial arrangement that may "raise a serious question about the integrity of the data," if FDA so determines. What is a serious question about the integrity of the data? Stating what the investigator must disclose and what types of action FDA may take when a serious question is raised provides insufficient guidance to industry. Without knowing where the bar they must clear is placed, it is a risky venture for a firm to hire an investigator who has a potential conflict that may not be found disqualifying by FDA until many years after the fact.

Given that it remains unclear how FDA uses this financial information, more is actually less with the issuance of this new Guidance. Ten years after the first Guidance was issued, FDA has yet to explain what it does with all the information it demands, and the standards by which FDA reviews and analyzes the information remains unclear. With a lack of transparency, it is difficult for industry to have any certainty. The purpose of a guidance should be to clarify and explain not only *what* FDA wants from an applicant but also *why* they want it and *how* the information will be used. Executive Order 13563, signed by President Obama on January 18, 2011, laid out the general principles of regulation, one of which is to "promote predictability and

reduce uncertainty" and "ensure that regulations are accessible, consistent, written in plain language, and easy to understand." FDA should keep these principles in mind when seeking to regulate clinical investigations and the disclosure of financial information of investigators. By requiring even more information to be submitted at considerable cost, without specifics as to how FDA uses that information, the Guidance does not promote predictability, reduce uncertainty, or provide transparency to the public.

III. Submission of Financial Information as Part of the Pretrial Application Process Would Create Additional Work for the FDA and Industry and Accomplish Little

WLF is pleased that FDA did not agree to the recommendation by the Inspector General that FDA require sponsors to submit financial information for clinical investigators as part of the pretrial application process. WLF agrees with FDA that requiring industry to collect and submit financial information prior to the application process would create significant additional work not only for industry but also for FDA, which would have to review the information before approving the trial. When only 1% of clinical investigators disclosed a financial interest of any kind as required by the regulations at the marketing application stage, it is clear that the burden of earlier disclosure is outweighed by the cost it would impose on industry and the FDA itself because FDA is already implementing other projects (through the HSP:BIMO Modernization Initiative) to strengthen oversight activities to safeguard research participants and the integrity of clinical trial data. Time and effort expended by industry and FDA over the course of many years

beginning at the pretrial process only to eventually deal with 1% of investigators who disclose a financial interest is a waste of resources, inefficient, and would accomplish little.

As stated in FDA's response to OIG's report, financial arrangements are but one consideration that FDA takes into account when considering potential sources of bias; there are many factors, such as design and number of investigators that are considered. The current FDA requirement that sponsors collect financial information prior to initiating a study is intended to assist the design of the study itself and how it is conducted. One way of doing this is through randomized assignment to treatment and blind studies. When a sponsor begins a study and even after a marketing application has been submitted to FDA for approval, the names and information of investigators may not yet be known. Information is submitted on an ongoing basis for months or years after the study begins and ends.

Requiring industry to collect and submit this information throughout a study would be unduly burdensome on sponsors of clinical trials. Implementing such a policy would require industry to continuously monitor investigators' financial arrangements for the duration of the study and to submit that information to FDA, and FDA correctly notes that this would burden the agency as well. Indeed, some investigators who participated early on in the process may not even be included in the marketing application. Moreover, not all clinical studies lead to marketing applications. As FDA pointed out to OIG, only 50% of Phase 3 drug trials are submitted for marketing and only 20% of device studies are submitted after completion. It would be an enormous waste of time, energy, and money for sponsors to collect information that, ultimately, they may never submit. While sponsors and investigators have a duty to minimize bias and

protect human subjects from harm, FDA's determination that submission of financial information at the pretrial application would be unnecessary is correct: it would provide little to no benefit in furthering those goals if financial information is sought pre-trial. The cost to industry in making the application process more complex could be astounding.

Finally, FDA's contention that requiring submission of this information in the pre-trial application would significantly burden FDA is crucial. This "significant burden" on administrative and review staff would require FDA to allocate resources that are better spent elsewhere, especially when FDA is already taking steps to provide greater oversight of clinical trials. When scrutiny over the amount of money spent on government by taxpayers is at a high level today, it is unfortunate that OIG seeks to burden FDA with even more paperwork without any discernible benefit in doing so. FDA is wise to reject this recommendation and should continue to require financial information at the marketing application stage and no sooner.

IV. FDA Should Err on the Side of Caution When Publicly Disclosing Financial Information

A proper balance between transparency and the right to privacy of clinical investigators with respect to financial arrangements is both an admirable goal and required by FDA's own regulations (21 CFR § 21). WLF strongly urges the agency to err on the side of caution when publicly disclosing financial information of clinical investigators, especially considering the information that may be disclosed concerning spouses and children. Public disclosure of certain information may rise to a violation of privacy rights of investigators and their families.

Moreover, disclosure could have a chilling effect on research and the willingness of the best researchers to participate in such research.

Ideally, there should be no public disclosure of the financial information of clinical investigators. This information is appropriately collected for the purpose of assisting the FDA in reviewing applications and has no place in the public sphere. However, if FDA goes forward with public disclosure, the best choice among the options in the proposed Guidance is to release a summary discussion of investigators' financial disclosures/certifications without revealing the specific financial interests and arrangements or the names of the investigators linked to those interests. The public may have a desire to know what types of interests are potentially influencing clinical trials, but it does not need to know the specifics of those interests or the specific investigators who have such interests.

The last thing that a clinical investigator or his/her spouse or child needs is public scrutiny of financial arrangements they may have made in the past that might factor into considerations of clinical trial bias. Even disclosure of the specific financial arrangements without disclosing the names of the investigators relating to those arrangements could place investigators or their family in a difficult situation. It is certainly possible that specific financial information could be connected to specific investigators by members of the public with less than noble intentions. This is not a risk worth taking, especially considering there is an alternative to disclosing specific information that would be as or more effective at informing the public. The small benefit that the public might derive from seeing the specifics of financial arrangements could be outweighed by the substantial harm that disclosing a person's private financial

arrangements might have on that person or his/her family. Certainly FDA has an interest in financial arrangements made by clinical investigators in order to assess data from a study. But the interest the public has in knowing the specifics of these financial details is minimal compared to the invasion of privacy that investigators and their families could potentially face if too much private financial data is made public. FDA has made it a practice to treat such information in confidence before and should not abandon this practice today.

A summary discussion is the superior choice among the alternatives because it allows the public to see what types of financial arrangements have been made between investigators and sponsors, without subjecting specific investigators, their spouses, and children to scrutiny. However, FDA must justify the need to disclose any type of financial information before adopting a policy that releases even a summary of such information. Privacy concerns should be the foremost consideration when the FDA adopts a policy on public disclosure of financial arrangements.

V. Conclusion

For the foregoing reasons, WLF respectfully requests that FDA revise its definition of "due diligence" by sponsors in collecting financial information, provide better guidance to industry in its review of financial information, maintain its position in opposition to the OIG recommendation that financial information be collected during the pretrial application process, and err on the side of caution with respect to privacy considerations of clinical investigators in any public disclosure of financial information.

Sincerely,

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Chairman and General Counsel

/s/ Michael P. Wilt
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Litigation Attorney