McDermott
Will & Emery

New FDA Draft Guidance Regarding Financial Disclosures by Clinical Investigators

July 11, 2011

New recommendations recently released by the FDA demonstrate the changing environment for conflicts of interest management and emphasize the need for pharmaceutical companies, medical device manufacturers and health care providers to ensure they have internal processes that adequately anticipate and meet the baseline requirements.

On May 25, 2011, the U.S. Food and Drug Administration (FDA) released a new draft guidance entitled *Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators* (Draft Guidance). Comments regarding this Draft Guidance are due to the FDA no later than July 25, 2011.

Though the Draft Guidance is not the final statement of the FDA's position on this topic, it provides an opportunity for the pharmaceutical and device industry, health care providers and institutions to evaluate their current conflict of interest programs and consider modifications to align their programs with these new anticipated standards. The Draft Guidance would revise and replace the FDA's 2001 publication, *Guidance for Industry: Financial Disclosure by Clinical Investigators* (the 2001 Guidance). The issuance of the Draft Guidance by the FDA suggests that the agency will be scrutinizing more closely investigator and institutional compliance in the management of conflicts of interest. In addition, the Draft Guidance clearly anticipates that investigators, institutions and industry will take meaningful and coordinated steps to implement the FDA's regulations, and such compliance may require a substantive, thorough and deliberative process that exceeds the simple administrative exercise of collecting forms.

Current Conflict of Interest Environment

The agency's renewed focus in this area and its clear direction to investigators, institutions and industry to develop robust compliance mechanisms that focus not merely on the disclosure of financial interests but the management of such relationships illustrates that conflict of interest compliance is front and center. Since the FDA issued the 2001 Guidance, there have been a number of developments with respect to conflicts of interest. For example, the Association of Academic Medical Centers (AAMC) and similar organizations have published guidelines relating to conflicts of interest in biomedical research that have pushed best practices well beyond the requirements of the 2001 Guidance. In addition, U.S. Congressional and nationwide media scrutiny of financial relationships between providers and industry have raised public awareness of, and concern over, such relationships. Further, state and federal "Sunshine Laws" require public disclosure of certain types of financial relationships between industry and providers and have made such relationships more transparent and available for review and comment. Finally, the U.S. Public Health Service (PHS) has identified a need for updated regulations governing the disclosure of financial interests and management of conflicts of interest in PHS-funded research, and issued proposed regulations on this subject on May 21, 2010. In light of these developments and in response to increased demands for the FDA to provide updated best practices, the FDA has issued the Draft Guidance.

Overview

Like the 2001 Guidance, the Draft Guidance is structured in a question-and-answer format designed to anticipate and respond to issues and concerns of the pharmaceutical and device industry, investigators and institutions serving as research sites. The Draft Guidance first sets forth information on regulations governing financial disclosure requirements and provides explanations as to the policies and processes behind these provisions. Throughout the discussion of these requirements, the FDA reiterates the need for entities to maintain conflict of interest reporting and management strategies that—at a minimum—satisfy these regulatory requirements.

The Draft Guidance next provides a detailed discussion of the types of financial interests subject to disclosure; the categories of individuals for which the applicant is responsible for disclosing financial arrangements; specific requirements for applicants and sponsors; the types of clinical studies to which these financial disclosure requirements apply; and a description of the FDA review and enforcement processes. Although in many cases the "answers" in the Draft Guidance mirror those in the 2001 Guidance, in several respects they provide important clarifications.

Finally, the lengths to which the FDA devotes to describing the conflicts of interest disclosure and management procedures that should be in place further underscore that pharmaceutical companies, medical device manufacturers and providers are all potentially subject to substantial research-related consequences if these types of processes are overlooked. As such, even though many of these entities currently have fraud and abuse reporting policies in place, the Draft Guidance and other recent conflict of

interest publications confirm that these policies may be insufficient on their own to address conflicts of interest, and a robust conflict of interest policy is now a baseline requirement for these entities' compliance programs.

A Closer Look at Changes Affecting the Medical Device and Pharmaceutical Industry

Conflict of interest management is not a burden born solely by investigators and institutions. As the AAMC noted in its *Report of the AAMC Task Force on Industry Funding of Medical Education to the AAMC Executive Council*, conflicts of interest can best be addressed through a "principled partnership" between the biomedical industry and providers. The Draft Guidance reflects this philosophy by devoting a substantial portion of the document to recommendations for pharmaceutical and device companies serving in their capacities as "Applicants" and "Sponsors." An Applicant is the entity that submits a marketing application or re-classification petition to the FDA for approval of a drug, device or biologic. A "Sponsor" is the entity that initiates and is ultimately responsible for a research study and/or the party providing financial or in-kind support for a particular study. Although the commercial repercussions for failing to comply with the FDA regulations may be most severe for Applicants (because the FDA may refuse to consider certain data necessary to establish that the product is safe and effective), this does not mean that only Applicants need to be mindful of these requirements. In many cases, the Applicant is not the Sponsor, and industry entities seeking to license or acquire other rights in a product will be looking to Sponsors to have complied with the FDA regulations at the time the studies were collected.

The Draft Guidance seeks to reiterate and clarify aspects of the 2001 Guidance that the FDA determined may have been unclear. For example, the Draft Guidance reiterates the following salient provisions of the 2001 Guidance:

- The Sponsor is required to collect information regarding certain financial interests or arrangements (listed at 21 C.F.R. § 54.4(a)(3)) for Clinical Investigators who are not full-time or part-time employees of the Sponsor. The Draft Guidance explains that the principal submissions to the FDA for these financial disclosures are FORMS FDA 3454 and 3455. FORM FDA 3454 requires the Applicant to certify that no financial interests or arrangements exist. In contrast, Applicants must use FORM FDA 3455 to disclose the financial relationships and to describe steps taken to minimize any bias stemming from these relationships. The Sponsor(s) should have recorded this information at the time that the study was conducted on any appropriate form, which could include a form developed for this purpose by the Sponsor. Since the management of any conflicts of interest may take place at the Sponsor level, it will be important for Applicants to have procedures in place to confirm the management strategies reported in FORM FDA 3455.

- The Draft Guidance clarifies the FDA's rationale for requiring Sponsors to obtain and report financial information for Clinical Investigators. Most important, the FDA explains that Sponsors are best positioned to inquire as to investigators' financial interests and collect this type of information. Since the Applicant may not always serve as the Sponsor of the study, companies that serve as Applicants must now ensure that they have adequate procedures in place to review and confirm the financial data collected by Sponsors.

The Draft Guidance also takes note of certain areas where the FDA is concerned there has been confusion and resulting potential non-compliance. These areas have often involved requirements or definitions that may have conflicted with those contained in other regulations and guidance. For example:

- The FDA goes to extensive lengths in the Draft Guidance to create a more robust definition of the "due diligence" required of Applicants who attest they have not obtained the financial disclosures required under the regulations. This is of particular interest because of the heightened standard in the Draft Guidance. For example, the Draft Guidance explains that Sponsors and/or Applicants must make at least two telephone calls to contact Clinical Investigators, and draft a written memorandum memorializing each call. This demonstrates that only in the most limited of circumstances will the FDA approve an Applicant's statement that it was unable to locate the necessary financial information for a Clinical Investigator. This new clarification of "due diligence" means that any Applicant must ensure it has proper procedures in place to confirm Sponsors' financial data collection procedures in order to avoid any rejection of an application by the FDA for lack of due diligence related to cited studies.

- Although the FDA maintains its position from the 2001 Guidance that it does not prescribe the precise methods that Sponsors must follow to collect financial information, the Draft Guidance explains that forms for collecting these data must go beyond information included on FORM FDA 3455. For example, the Draft Guidance indicates that forms provided to Clinical Investigators must require them to submit financial information regarding spouses and dependent children. This requirement is one of many that underscores the need for Applicants to ensure that they confirm and trust the financial disclosure

procedures followed by each Sponsor. By way of example, a well-established, large pharmaceutical company serving as an Applicant that purchases the rights to market a drug or medical device developed by a smaller biotech Sponsor will want to be sure that the Sponsor's reporting procedures were adequate to capture all required financial disclosures and manage any reported financial interests, or risk rejection of certain data included in the marketing application.

- On a related note, the Draft Guidance specifically enumerates ways in which Sponsors can minimize the risk of bias from a conflict of interest so that they may continue to use a study in a marketing application (e.g., using randomization and blinding in a study). The FDA encourages Sponsors to work with it to minimize these biases. This type of symbiotic relationship with the FDA may suggest the agency will play an increasing role in reviewing and determining the sufficiency of Sponsor's and Applicant's management strategies. As such, the conflict of interest policies and procedures of these institutions will likely be subject to increased scrutiny by the FDA.

- The FDA specifically recommends that Sponsors collect financial disclosure information for most clinical studies in the event that they are later used in a marketing application. By making this recommendation, the FDA essentially articulates the need for all organizations acting in a Sponsor capacity to have robust conflict of interest reporting procedures in place. As discussed above, this type of statement by the FDA necessitates that entities review their conflict of interest processes to ensure they will be compliant with this more stringent reporting environment.

The Draft Guidance does not necessarily address all outstanding issues. For example, there is no discussion in the Draft Guidance as to whether Applicants would be required to disclose financial or other interests reported under an Applicant's or institution's conflict of interest program in the event that the program has more stringent requirements than those set forth in the Draft Guidance (e.g., requiring Clinical Investigators to disclose any equity interest in a publicly held company that is less than $50,000, or defining the term "conflict of interest" more broadly for reporting purposes). This is in contrast to guidance issued by PHS for federally funded research, which explicitly require an entity with more stringent financial disclosure requirements to disclose to PHS the same financial interests that must be reported under the entity's conflict of interest policy. However, Sponsors and Applicants should exercise caution as they navigate overlapping and potentially inconsistent systems and regulations.

There is an overarching theme throughout the Draft Guidance that Sponsors and Applicants should have programs to identify and manage conflicts, and the FDA expects Applicants to be able to provide all required financial information. These significant developments and changes to the 2001 Guidance confirm the importance of ensuring that pharmaceutical companies have a working knowledge of the Draft Guidance so they are best positioned to review their own conflict of interest programs and make any necessary changes to meet these new Federal standards.

What the Draft Guidance Means for Providers

The Draft Guidance also includes important revisions applicable to providers as they implement their systems for reporting and recording financial and proprietary interests of physicians and other appropriate health care personnel. Providers should carefully review the requirements for Sponsors and Applicants insofar as there are circumstances where a provider may also serve as a Sponsor; and these new recommendations, if implemented, may lead to revised conflict of interest procedures for pharmaceutical companies and medical device manufacturers that would require providers to change reporting policies and record retention protocols accordingly.

Several revisions to the 2001 Guidance warrant the thorough review of institutions functioning as coordinators of studies, and provide unique recommendations for these entities as they develop and conduct research studies:

- The Draft Guidance seeks to clarify and refine the definition of Clinical Investigator from the 2001 Guidance. Many had concluded that the term Clinical Investigator was limited to the individual serving in the role of "Principal Investigator," or lead investigator, on a study. The Draft Guidance clarifies the FDA's understanding of the term Clinical Investigator by noting that it is broader for financial disclosure regulations as compared to other regulations that more focus on a Principal Investigator function. However, the Draft Guidance also emphasizes that the term is not intended to include "hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data." In this regard, the FDA is taking a narrower approach to identifying individuals who should report financial interests for consideration as compared to prevailing best practices set forth in guidance by the AAMC and other organizations.

- The Draft Guidance provides important new information about factors FDA will consider in mitigating any action that should be taken against a study. A representative list of these factors includes: the total number of investigators and subjects in the study; the number and percentage of subjects enrolled by the investigator with the conflict of interest; the design of the clinical study; the method of evaluation; and the results of the investigator disclosing the interest as compared to the results of other investigators. Although none of the factors is dispositive, institutions that are responsible for conducting these studies must ensure they consider and fully understand each of these conflict-minimizing strategies. This new list of factors in the Draft Guidance reiterates the FDA's expectation that institutions have well-developed management policies in place, and should also create heightened awareness among providers to minimize any risk that they lose funding or support from Sponsors as a result of failing to address proactively these types of strategies.

- The Draft Guidance significantly revises the FDA's interpretation of "due diligence" in collecting information from Sponsors. In practice, Sponsors often look first to institutions and providers to collect and maintain these financial data for their Clinical Investigators. Thus, it is imperative these institutions collect and retain all financial data in accordance with the guidelines in the Draft Guidance. By neglecting to follow these new recommendations to capture more information than the FDA Disclosure Forms and minimize bias resulting from any financial relationships, institutions will be unable to demonstrate to Sponsors and Applicants that they have adequate procedures in place to make them an appropriate venue for conducting these studies.

A final consideration is how providers will design a conflict of interest policy to combine the reporting requirements under the Draft Guidance with other Federal statutory and regulatory requirements in place, and industry best practices. For example, institutions designing conflict of interest programs will want to consider:

- The interaction of the Draft Guidance with the more stringent requirements under the proposed PHS requirements, which would require reporting of certain financial interests greater than $5,000 (but still less than the FDA's reporting threshold of $0 for certain compensation arrangements). In addition, institutions must look to the best practices set forth in AAMC guidances, which focus not only on requiring reporting of physician conflicts of interest but also mandate reporting of institutional conflicts of interest.

- The effect of the heightened due diligence standard for Applicants trickles down to procedures that institutions and other providers must implement to satisfy these obligations. Specifically, Applicants and Sponsors will look to providers to collect these data from physicians and other individuals qualifying as Clinical Investigators. As such, institutions must comply with all aspects of the Draft Guidance—even those requirements directed specifically to Applicants and Sponsors—so that these entities may demonstrate they have conducted "due diligence" on behalf of these entities.

Conclusion

The recommendations set forth in the Draft Guidance demonstrate the constantly changing and evolving environment for conflicts of interest management. The interplay of the various statutes, regulations, guidance and emerging best practices emphasizes the need for pharmaceutical companies, medical device manufacturers and health care providers to ensure they have internal processes in place that adequately anticipate and meet these new baseline requirements. For more information, please contact your regular McDermott lawyer, or:

Jennifer Geetter and Elizabeth Isbey

Jennifer Geetter: +1 202 756 8205 jgeetter@mwe.com

Elizabeth Isbey: +1 202 756 8283 eisbey@mwe.com

For more information about McDermott Will & Emery visit www.mwe.com