POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

NDAs/BLAs: Financial Disclosure

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PURPOSE

- This MAPP establishes policies and procedures for review staff in the Office of New Drugs (OND) for the review and management of financial disclosure information submitted in new drug applications (NDAs), biologics license applications (BLAs), and supplemental applications to NDAs and BLAs.

BACKGROUND

- On February 2, 1998, FDA published a final rule requiring applicants who submit marketing applications for any drug, biological product, or device to submit certain information concerning the compensation to, and financial interests of, any clinical investigator or subinvestigator conducting the types of clinical studies covered by the rule.[1]

- These requirements, which became effective on February 2, 1999, apply to any covered clinical study submitted in a marketing application that the applicant or FDA relies on to establish that a drug product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety. In addition, financial information is required for any covered clinical

[1] See the final rule "Financial Disclosure by Clinical Investigators" (63 FR 5233). This final rule was amended on December 31, 1998 (63 FR 72171).

study submitted after February 2, 1999, as part of an amendment or resubmission to a previously submitted application.

- The final rule requires applicants to certify, using Form FDA 3454, to the absence of certain financial interests of clinical investigators and subinvestigators in covered studies or to disclose those financial interests, using Form FDA 3455. If the applicant does not include certification, disclosure, or both, if appropriate, or does not certify that it was not possible to obtain the information, FDA may refuse to file the application.

- The regulation is intended to ensure that financial interests and arrangements of clinical investigators or subinvestigators that could affect the reliability of data submitted to FDA are identified and disclosed by the applicant. On December 31, 1998, FDA published an amended final rule. The changes to the final rule resulted in a reduced burden for gathering certain financial information for studies completed before February 2, 1999.[2]

- In March 2001, FDA issued the guidance for industry *Financial Disclosure by Clinical Investigators* to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing financial disclosure by clinical investigators. To address issues raised by the Office of Inspector General, Department of Health and Human Services,[3] as well as questions FDA received from industry and the public, FDA revised the 2001 guidance in May 2011. In February 2013, FDA finalized the 2011 draft guidance with the guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators*.[4]

POLICY

- During drug development, OND will encourage sponsors to work with the review team and clinical investigators to ensure that potentially covered clinical studies are sufficiently well designed and conducted to minimize potential bias should financial arrangements (e.g., equity interest in the sponsor of the study, proprietary interest in the drug product under investigation) of clinical investigators or subinvestigators subsequently be identified. If a sponsor informs FDA of such financial interests or arrangements, these will be identified as

[2] See the amended final rule "Financial Disclosure by Clinical Investigators" (63 FR 72171).

[3] See the report OEI-05-07-00730, The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information, available at https://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

agenda items for discussion at end-of-phase 2, pre-IND, and pre-NDA meetings, if appropriate.

- The OND regulatory project manager (RPM) will conduct and electronically archive administrative filing reviews of marketing applications to ensure that financial disclosure information has been submitted. If financial disclosure information is required but was not submitted, and the applicant has not documented due diligence to collect financial disclosure information, the RPM will notify the applicant to submit the missing information before the filing date.

- At the time of filing of the marketing application, the medical reviewer will ensure that financial disclosure information has been submitted on the appropriate FDA forms. The adequacy of the submitted information will be determined during the course of the medical review.

- A refuse-to-file action or complete response action, based solely on inadequate financial disclosure information, will not be taken without first consulting with the OND Immediate Office (IO).

RESPONSIBILITIES AND PROCEDURES

OND Regulatory Project Managers will:

- During the administrative review of original, resubmitted, amended, and supplemental applications for which financial disclosure information is required, ensure that financial disclosure information has been submitted.

- Notify the applicant when required financial disclosure information is not included in the application and instruct the applicant to submit the information. If the clinical reviewer determines that submitted financial disclosure information is not adequate, notify the applicant that additional information is required.

- With the medical review team, notify the Office of Scientific Investigations (OSI) when it appears the financial arrangements disclosed may have affected the interpretation of study results or otherwise affected the reliability of the data.

- Forward to the OND IO questions on financial disclosure, including refuse-to-file questions and requests for waivers, that cannot be addressed at the division or office level and are not addressed in Attachment 1, Frequently Asked Questions.

OND Medical Reviewer with Team Leader and Division Director, as needed, will:

- Ensure that financial disclosure information is provided for all covered clinical studies in an application and notify the RPM if financial disclosure information has not been submitted for studies meeting the definition of covered clinical study

- Review the submitted financial disclosure information:

  – Following the prompts in the financial disclosure review section of the clinical review template, evaluate the financial disclosure information provided in the application and document the findings in the clinical review. This includes determining and documenting whether an appropriate certification and, where applicable, complete information on any arrangements or interests is provided for all investigators and subinvestigators participating in all covered clinical studies.

  – Where financial interests are disclosed for any clinical investigators or subinvestigators of covered clinical studies, document and discuss any steps taken by the study sponsor or other parties to minimize bias, for example, through study design (e.g., methods of blinding, method of evaluation, randomization), through the number of clinical investigators and study sites (thus minimizing the effect of any particular investigator), and substantiation or lack of substantiation of study results.

  – Evaluate and document whether the data are questionable/suspect from any investigators or subinvestigators for which financial arrangements have been disclosed (e.g., data from disclosing investigator are more favorable than that from other investigators/centers).

- If the results/data reported by any clinical investigator or subinvestigator that disclosed financial arrangements are questionable (e.g., data from the investigator are more favorable than that from other investigators), perform one or more of the following:

  – Via the RPM:

    ▪ Consult OSI about a possible site visit

    ▪ Request that the applicant submit further analyses of the data (e.g., an analysis of the study omitting the investigator's data)

  – Make a recommendation to the division (or office) director on whether the data from the covered clinical study can be considered in the determination of the regulatory action on the application

  - Discuss with the division (or office) director whether the need for additional independent studies to confirm the results of the study in question should be identified as an approval deficiency

  - If the recommendation is to exclude specific data from the evaluation of the application, discuss the recommendation with division management and, if the application is for office-level signature, office management

- In the medical review, summarize the financial disclosure review findings and any action(s) taken as a result of the review of the financial disclosure information

Office of Scientific Investigations will:

- If consulted, consider the seriousness of the questions raised and, when appropriate, generate an inspection assignment to evaluate pertinent records from the sponsor, applicant, and/or clinical investigator(s) in question

REFERENCES

1. Guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators*

2. 21 CFR part 54

DEFINITIONS

Note that the definitions in 21 CFR part 54, provided below, differ from those in 21 CFR parts 312 and 314. See the guidance for clinical investigators, industry, and FDA staff* Financial Disclosure by Clinical Investigators *for additional details regarding the comparisons of certain terms.

- **Clinical Investigator:** Any investigator or subinvestigator directly involved in the treatment or evaluation of research subjects. For the purposes of financial disclosure, the definition includes the spouse and each dependent child of the investigator.

- **Covered Clinical Study:** Any study of a drug, biologic, or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the drug product is effective (including studies that show equivalence to an effective drug product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. In general, this does not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy

determination), large open safety studies conducted at multiple sites, or expanded access protocols.

- **Sponsor of a Covered Clinical Study:** The party supporting a particular study while it was carried out (21 CFR 54.2). This includes a party providing partial support, such as a drug company providing the drug product for a study conducted by the National Institutes of Health or Veterans Administration. A covered clinical study can have more than one sponsor for purposes of part 54.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment 1: Frequently Asked Questions

Q1. The effective date for submission of financial disclosure information in marketing applications was February 2, 1999. What financial disclosure information must applicants provide for studies begun before that date, but not submitted in a marketing application until after that date?

A. Four types of financial payments are covered under the financial disclosure rule. The information that must be submitted is based on the date the study was completed, not the date it began.

1. **Outcome Payments** (payment dependent on outcome of the study)
   Study completed before 2/2/99: REQUIRED
   Study completed after 2/1/99: REQUIRED

2. **Proprietary Interest** (e.g., patents/trademark/copyright/licensing agreement in the drug product)
   Study completed before 2/2/99: REQUIRED
   Study completed after 2/1/99: REQUIRED

3. **Equity Interest** (e.g., stock ownership, stock options)

   a. For publicly traded companies (interest greater than $50,000 during the time the investigator is conducting the study and for 1 year following completion of the study)
      Study completed before 2/2/99: NOT REQUIRED (for multicenter studies, all sites must have been completed before 2/2/99)
      Study completed after 2/1/99: REQUIRED

   b. For nonpublicly traded companies (i.e., whose value cannot be easily determined) (need to report *any* equity interest)
      Study completed before 2/2/99: REQUIRED
      Study completed after 2/1/99: REQUIRED

4. **Significant Payments of Other Sorts (SPOOS)** (e.g., honoraria, consultation fees, research grants, compensation in the form of equipment) that have a total value of greater than $25,000 (during the time the investigator is conducting the study and for 1 year following completion of the study), exclusive of payments for conducting the clinical study or other clinical studies
   Study completed before 2/2/99: NOT REQUIRED
   Study completed between 2/2/98 and 2/1/99: Report payments made between 2/2/99 and study completion date plus 12 months
   Study completed after 2/1/99: REQUIRED

Q2. The marketing application was submitted less than 1 year after completion of the covered studies. The regulation states that investigators must provide financial disclosure information during the course of the study and for 1 year after its completion. Does the applicant have to amend the application with updated financial disclosure information?

A. No. The applicant needs to report only when the data from the covered study are submitted. However, under the regulation, investigators must promptly update their financial information, if relevant changes occur during the course of the investigation or for 1 year following completion of the study. Sponsors and applicants are responsible for keeping updated financial information from investigators in their files.

Q3. The original application was submitted before February 2, 1999, but was not approved in the first cycle. The application was amended with a new efficacy study that is essential to approval. Is financial disclosure information required for the investigators for this new study?

A. Yes. Financial disclosure information must be submitted for all covered clinical studies submitted on or after February 2, 1999.

Q4. The division just received an original new drug application. The covered clinical studies were completed before February 2, 1998. Does any financial disclosure information have to be included in the application?

A. Yes. The application must contain information on outcome payments and proprietary interests. If a nonpublicly traded company sponsored any studies, information on equity interest in that sponsor must also be submitted. (See the amended final rule "Financial Disclosure by Clinical Investigators"; 63 FR 72172 – 72173.)

Q5. The division just received an original new drug application. The covered clinical studies were completed May 31, 1998. Does any financial disclosure information need to be included in the application?

A. Yes. The application must contain information on outcome payments, proprietary interests, and equity interests for any studies sponsored by a nonpublicly traded company. Also, SPOOS made between February 2, 1999, and May 31, 1999, must be reported. (See the amended final rule "Financial Disclosure by Clinical Investigators"; 63 FR 72172 – 72173.)

Q6. The applicant submitted only a Form FDA 3454 with a long list of investigators appended. The applicant did not submit a Form FDA 3455. Is this sufficient?

A. It may be, if none of the clinical investigators who participated in the covered clinical studies for the application had reportable interests, and if each of them is included on the list appended to Form FDA 3454. Investigators who are full- or part-

time employees of the study sponsor may be identified separately (rather than on either form).

Q7. Do applicants have to provide the names of all investigators who reported no financial interests?

A. Yes. The applicant can submit a single completed Form FDA 3454 for all clinical investigators certifying to the absence of financial interests and append a list of those investigators to the form.

Q8. What does the applicant have to submit for investigators who did not provide financial disclosure information to the applicant?

A. For studies initiated by the applicant and completed before February 2, 1999, the applicant must certify that it was unable to obtain the information despite due diligence in attempting to obtain it. The applicant should explain in the certification the steps it took to show due diligence in trying to obtain the information. Even if not all information is available, the applicant must submit Form FDA 3455 for each nonresponding investigator that discloses any outcome payments, proprietary interest, equity interest (for nonpublicly traded companies), and SPOOS. It is expected that the applicant will have this information in its company files.

For studies sponsored by another party, the applicant must certify on Form FDA 3454 that it acted with due diligence to obtain from the listed investigators the required information and was not able to obtain it. For each investigator who did not respond, the reason information could not be obtained should be provided.

Q9. Is financial disclosure information required for foreign investigators?

A. Yes. For clinical studies conducted under an investigational new drug application (IND), financial disclosure information must be collected from all investigators, foreign and United States, before the investigator is permitted to participate in the study (21 CFR 312.53(c)(4)).

For clinical studies not conducted under an IND, the applicant must submit financial disclosure information in the marketing application. If the applicant is unable to obtain this information from the investigator, the applicant must submit documentation of its efforts to obtain this information with due diligence from the investigator.

Q10. What needs to accompany Form FDA 3455?

A. A description of the steps taken to minimize the potential for bias resulting from any of the disclosed interests.

Q11. Do investigators have to report only that they and/or their families have a financial interest that exceeds the threshold limit for equity interests for SPOOS?

A. No. The investigator should also provide specific information as to the nature and size of the interest, such as who is the owner of equity interest (investigator, spouse, or child) and what the payments covered.