POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

NDAs/BLAs: Financial Disclosure

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PURPOSE

- This Manual of Policies and Procedures (MAPP) establishes policies and procedures for review staff in the Center for Drug Evaluation and Research (CDER) for the review and management of financial disclosure information submitted in new drug applications (NDAs), biologics license applications (BLAs), supplemental applications to NDAs and BLAs, and over-the-counter (OTC) monograph order requests (OMORs).[1,2]

BACKGROUND

- On February 2, 1998, the Food and Drug Administration (FDA) published a final rule requiring applicants who submit applications for any drug, biological

[1] As used in this MAPP, "financial disclosure information" means:
- Certification, using Form FDA 3454, that either no financial interests or arrangements exist or that the applicant acted with due diligence but was unable to obtain the information;
- Disclosure, using Form FDA 3455, of the nature of disclosable financial interests and/or arrangements; or
- Both certification and disclosure.

Refer to 21 CFR 54.4 for more information.

[2] OTC monograph order request (OMOR) refers to a request for FDA to issue an administrative order under section 505G(b)(5) of the FD&C Act. See also section 744L(7) of the FD&C Act. For the purposes of this MAPP, the term "application" includes NDAs, BLAs, and OMORs and any associated supplemental applications.

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.[3,4]

- These requirements, which became effective on February 2, 1999, and were codified in FDA regulations in 21 CFR 54, apply to any covered clinical study submitted in an application that the applicant or FDA relies on to establish that a 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 study submitted after February 2, 1999, as part of an amendment or resubmission to a previously submitted application.

- To meet the requirements of the regulation, an applicant must:

  – Certify, using Form FDA 3454, to the absence of certain financial interests of clinical investigators in covered studies or certify that it was not possible to obtain the information described in the regulation;

  – Disclose certain financial interests, using Form FDA 3455; or

  – Both certify and/or disclose, as applicable.

  If the applicant does not include certification or disclosure, 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.[5]

- In March 2001, FDA issued the guidance *Financial Disclosure by Clinical Investigators* to assist clinical investigators, industry, and FDA staff in interpreting and complying with regulations governing financial disclosure by clinical investigators. To address issues raised by the Office of Inspector General, Department of Health and Human Services, as well as questions FDA received from industry and the public, FDA revised the 2001 guidance in May 2011.[6] In

[3] For the purposes of this MAPP, the term *"applicant"* also includes an OMOR requestor.
[4] See the final rule *"Financial Disclosure by Clinical Investigators"* published on February 2, 1998 (63 FR 5233); this final rule was amended on December 31, 1998 (63 FR 72171). See also 21 CFR 54 and 21 CFR 314.50(k).
[5] See 21 CFR 54, 21 CFR 314.50(k).
[6] 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.

February 2013, FDA finalized the 2011 draft guidance with the guidance *Financial Disclosure by Clinical Investigators* (Feb 2013).[7]

- On March 27, 2020, the President signed into law the Coronavirus Aid, Relief, and Economic Security Act (CARES Act). The CARES Act added section 505G to the FD&C Act. Section 505G reforms and modernizes the framework for the regulation of OTC monograph drugs.[8] Under the process set forth in section 505G(b) of the FD&C Act, FDA has the authority to issue a final order that adds, removes, or changes generally recognized as safe and effective (GRASE) conditions for an OTC monograph drug. A requestor can initiate the order process by submitting an OMOR with respect to certain drugs, classes of drugs, or combinations of drugs. FDA regulations require financial disclosure information for a covered clinical study to be submitted as part of an OMOR.[9]

POLICY

- As part of the application review process, the Office of New Drugs (OND) Clinical review staff evaluates financial disclosure information submitted for all clinical investigators who conducted covered clinical studies. This is to determine whether there are potential sources of bias that could impact the reliability of data. OND evaluates whether financial disclosure information is properly submitted and completed. When applicable, OND evaluates if financial interests or arrangements of clinical investigators raise serious questions about the reliability of the data derived from the covered clinical study.

- The final decision for a refuse-to-file action or complete response action, based solely on inadequate financial disclosure information, is determined by the OND Clinical review division (or office) director.[10] However, the OND Immediate Office (IO) should be consulted before the refuse-to-file action or complete response action is taken.

PROCEDURES

General

[7] For the most recent version of a guidance, refer to the *Search the FDA Guidances* webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[8] OTC monograph drugs may be marketed without an approved drug application under section 505 of the FD&C Act if they meet the requirements of section 505G of the FD&C Act, as well as other applicable requirements.
[9] See 21 CFR 330.10(f).
[10] For more information regarding refuse to file actions, refer to 21 CFR 314.101 – *Filing an NDA and receiving an ANDA*. For more information regarding complete response actions, refer to 21 CFR 314.110 – *Complete response letter to the applicant*.

- OND Clinical review staff evaluates financial disclosure information submitted for all clinical investigators who conducted covered clinical studies. This is to determine if there are potential sources of bias that could impact data reliability.

- A "covered clinical study" means any study of a drug or device in humans that the FDA relies on to establish that the product is effective including studies that show equivalence to an effective product or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l 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, treatment protocols, and parallel track protocols.

- "Clinical investigator" means a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

- Disclosable financial interests, arrangements, and payments that must be disclosed are described below.

  – Any compensation made to the clinical investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.

  – A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright, or licensing agreement.

  – Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

  – Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest exceeds $50,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

  – Significant payments of other sorts (SPOOS) are payments that have a cumulative monetary value of $25,000 or more and are made by any sponsor of a covered study to the investigator or the investigator's institution during the time the clinical investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator (e.g., a grant to the investigator or to the institution to fund the investigator's ongoing research or compensation in the

form of equipment), exclusive of the costs of conducting the clinical study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria.

OND/Office of Regulatory Operations (ORO) Project Management Staff:

- Ensures financial disclosure information is submitted on the appropriate FDA forms (e.g., FDA Form 3454 or 3455) for applications in which financial disclosure is required.[11] This evaluation will be included in the Regulatory Project Manager (RPM) filing review.

- Notifies the applicant when required financial disclosure information is not included in the application, and instructs the applicant to submit the information. If the clinical reviewer determines the submitted financial disclosure information is not adequate, ORO staff notifies the applicant of the additional information required.

- Notifies the Office of Scientific Investigations (OSI) when the clinical review team identifies disclosed financial arrangements that may impact the reliability of the data.

- Forward questions on financial disclosure that cannot be addressed at the division or office level and are not addressed in *Attachment 1: Frequently Asked Financial Disclosure Questions,* to the Office of Regulatory Policy (ORP) at CDERORPRequests@fda.hhs.gov.

OND Clinical Review Staff (Reviewer, Team Leader and/or Division or Office Director (as needed)):

- Ensure financial disclosure information is provided for all clinical investigators who conducted covered clinical studies in an application. Notifies ORO staff if financial disclosure information is not submitted for all clinical investigators who conducted 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 review template, evaluate the size and nature of the financial disclosure information provided in the application, and document the findings in the review. This includes determining and documenting whether appropriate certifications and/or complete disclosures of any financial interests or arrangements are provided for all clinical investigators participating in all covered clinical studies.

[11] Current versions of all FDA forms are available on the *Forms* webpage: https://www.fda.gov/about-fda/reports-manuals-forms/forms.

- When financial interests are disclosed for clinical investigators of covered clinical studies, document and discuss steps taken by the applicant 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 financial interests of any clinical investigator raise serious questions about the reliability of the data (e.g., data from disclosing clinical investigator are more favorable than that from other investigators/study sites).

- If serious questions about the reliability of the data reported by any clinical investigator who disclosed financial arrangements arise (e.g., data from the investigator are more favorable than that from other investigators), perform one or more of the following:

  - Via ORO staff:

    - Contact OSI about a possible clinical investigator inspection.

    - Request that the applicant submit further analyses of the data (e.g., to evaluate the effect of the clinical investigator's data on overall study outcome, such as an analysis of the study omitting the investigator's data).

  - 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 a deficiency in a complete response letter.

  - If applicable, make a recommendation to the OND Clinical review division (or office) director on if the data from the covered clinical study should not be considered in the determination of the regulatory action on the application.

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

- In the application review, summarize the financial disclosure review findings and actions taken as a result of the review of the financial disclosure information. If the OND Clinical review division (or office) director determines that a refuse-to-file or complete response action is warranted based solely on inadequate financial disclosure information, OND Clinical review staff will consult the OND IO prior to taking such action.

Office of Compliance (OC)/Office of Scientific Investigations (OSI)

- If contacted at any time regarding concerns related to financial disclosures, OSI will collaborate with the OND Clinical review division to consider the seriousness of the questions raised and determine whether inspections are needed to evaluate pertinent records from the sponsor, contract research organization (CRO), and/or the clinical investigator(s), as necessary and appropriate.

REFERENCES

- The Food, Drug, and Cosmetics (FD&C) Act, Sections 505G and 744L (7)
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 312: Investigational New Drug Application
- 21 CFR 314.50: Content and format of an NDA
- Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (February 2013)

DEFINITIONS

Note that the definitions in 21 CFR 54, provided below, differ from those in 21 CFR 312 and 314. See the guidance *Financial Disclosure by Clinical Investigators* (Feb 2013) for additional details regarding the comparisons of certain terms.

- **Clinical Investigator:** means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. For the purposes of financial disclosure, the term also includes the spouse and each dependent child of the investigator.[12]
- **Covered Clinical Study:** means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to 21 CFR 54(e) that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l 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, treatment protocols, and parallel track protocols. An applicant may

[12] 21 CFR 54.2(d).

consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.[13]

- **Significant payments of other sorts (SPOOS):** means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study.[14]

- **Sponsor of the Covered Clinical Study:** means the party supporting a particular study at the time it was carried out.[15]

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
06/21/2017	Initial	
10/9/2024	1	Updated to align with current OND organizational structure, applicable user-fee agreements (UFA) commitments, and contemporary CDER workflow procedures and best practices.

[13] 21 CFR 54.2(e).
[14] 21 CFR 54.2(f).
[15] 21 CFR 54.2(h).

ATTACHMENT 1: Frequently Asked Financial Disclosure Questions (FAQs)

Q1. What is the purpose of FDA's review of clinical investigator financial disclosure information and how can sponsors minimize bias?[16]

A: FDA's review of clinical investigator financial disclosure information alerts FDA staff to financial interests and arrangements that could lead to bias in covered clinical studies. The financial disclosure process also provides FDA with information regarding whether and to what extent the sponsors have taken steps to minimize the risk of bias.

An important means of minimizing the potential for bias resulting from such financial interests and arrangements is through proper study design (see 21 CFR 54.5(b)). For example, using randomization and blinding helps to minimize the potential for bias in assigning subjects to receive the test article or placebo and in assessing study outcomes and analyzing results. Similarly, having someone with no financial interests or arrangements evaluate study endpoints, especially in an unblinded study, can help minimize potential bias in assessing therapy outcomes. FDA staff consider the financial disclosure information and the methods the sponsor used to minimize bias during the review of marketing applications to assess the reliability of the clinical data (see 21 CFR 54.1). Additionally, because sponsors of studies conducted under INDs and IDEs are required to collect financial information from clinical investigators prior to study initiation, sponsors can work with FDA to minimize any potential bias. FDA strongly encourages sponsors of studies not conducted under an IND/IDE to collect financial information prior to study initiation for the same reasons.

Q2. Where in a marketing application for a drug or a biological product should an applicant include the certification or disclosure forms and attachments?[17]

A: Applicants using the format described in Form FDA 356h (Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use) should include the clinical investigator list and financial certification and/or disclosure forms and attachments as part of item 19 (Financial Information) of the application. Applicants using the Common Technical Document (CTD) format should include this information in Module 1.3.4.10.

Q3: How should the financial information be submitted?[18]

A: The financial information is required to be submitted using Forms FDA 3454 and/or 3455 (21 CFR 54.4(a)), which are available online.

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[16] Q1 corresponds to question A.2 in the Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (Feb 2013).
[17] Q2 corresponds to question B.3 in the Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (Feb 2013).
[18] Q3 corresponds to question B.5 in the Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (Feb 2013).

Q4: What does FDA mean by the term "due diligence"?[19]

A: "Due diligence" is a measure of activity expected from a reasonable and prudent person under a particular circumstance, in this case, collecting information about financial interests or arrangements. FDA expects that applicants will typically be able to obtain the required information because investigators are required to provide financial disclosure information to sponsors before participating in a clinical study (21 CFR 54.4, 312.53(c), 812.43(c) and 812.20(b)(5)). In the rare circumstance where applicants are unable to obtain required financial information, applicants must certify that they acted with due diligence and explain why the information was not obtainable (21 CFR 54.4). If all of the information required to make a complete certification or disclosure is not available from a sponsor, applicants should make appropriate efforts to obtain the information by other means. That may mean contacting an individual investigator or subinvestigator directly.

If an investigator's whereabouts are unknown, for example because the investigator left a study prior to its completion or prior to one year following completion of the study, FDA recommends that sponsors and/or applicants try to locate the clinical investigator. Sponsors and applicants should exercise reasonable judgment regarding the appropriate amount of effort to expend when attempting to contact investigators, which may include consideration of the role of the investigator in the study and the importance of the investigator's data contribution. In most cases, FDA suggests that more than one attempt at contacting an investigator would be appropriate and that more than one method of contact be attempted. FDA also recommends that each attempt to contact the investigator be documented, for example, by maintaining copies of e-mails and letters and documenting telephone calls and conversation by written memoranda. FDA also suggests that sponsors and applicants consider using a method of contacting investigators that allows verification of receipt, such as certified mail or reliable courier service that provides notice of recipient's receipt of a letter. When such methods are used, copies of the delivery notice or undeliverable notice should be maintained.

If an investigator is no longer at the institution where the study was conducted, FDA recommends that the sponsor or applicant make a reasonable attempt to locate the investigator, for example, by requesting contact information from the institution where the study was conducted or the institution with which the investigator was affiliated, contacting professional associations the investigator may have been affiliated with, and/or conducting Internet searches. If a clinical investigator cannot be located or information for some other reason cannot be obtained from the investigator, the sponsor should have access to certain disclosable financial information and arrangements, for example, payments made specifically to the investigator or information related to product sales that may generate royalties due to the investigator. On request from an applicant, sponsors should check their records for such information and, subject to any privacy laws (noting that other countries' laws may differ from United States law), the sponsor should

[19] Q4 corresponds to question B.7 in the Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (Feb 2013).

then provide disclosable information to the applicant. In addition, and as necessary, efforts should be made to obtain disclosable financial information from other reasonably available, reliable, public sources of information. For example, information on proprietary interests in the test product, such as patents and trademarks, should be available from publicly available sources. Another possible source of information is the clinical investigator's institution, which may have collected financial information and, if consistent with their policies, may release this information to the applicant upon request.

Appropriate certifications, disclosures, and/or explanations should be provided to FDA on the basis of information obtained. See Question F.2 for additional information.[20] An applicant must exercise due diligence whether a covered study is conducted at foreign or domestic sites. The agency expects that a reasonable and prudent applicant will take affirmative steps at the first opportunity to see that the financial information required for a complete certification or disclosure under 21 CFR 54 is collected and maintained. This is not only to ensure that the applicant will be able to make a complete submission but also to ensure that the study sponsor will take steps to protect the study against possible bias. See Questions E.3, E.5, and F.3 for additional information.[21]

Q5: How is the review to be documented?[22]

A: Each FDA Center provides review templates or checklists for their review staff to use that include a section on financial disclosure issues. In general, the review should document that a list of clinical investigators for each covered clinical study was provided, and that, as applicable, there was either certification or documentation of disclosable financial interests and arrangements for each investigator on the list who is not an employee of the sponsor (21 CFR 54.4). When a disclosure of financial interests and arrangements is included (Form FDA 3455), reviewers should ensure that the details of the disclosable financial interests and arrangements are attached to the forms along with a description of the steps the sponsor has taken to minimize the potential bias of clinical study results by any of the disclosed interests or arrangements (21 CFR 54.4(a)(3)). The reviewer will address the question of whether these interests and arrangements raise serious questions about the integrity of the data and describe any actions taken to minimize bias. The reviewer will also describe any actions taken by the agency to address any questions raised by a disclosable financial interest or provide an explanation for why no action was indicated (21 CFR 54.5). This documentation should be included in the appropriate section of the review template. When a sponsor certifies that he/she acted with due diligence to obtain information regarding the clinical investigator's financial interests and arrangements but was unable to obtain it, reviewers should ensure that an explanation of the reason why the information could not be obtained and the efforts made to obtain the information is attached to the Form FDA 3454 (21 CFR 54.4).

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[20] Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (February 2013).
[21] Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (February 2013).
[22] Q5 corresponds to question H.5 in the Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators* (Feb 2013).

Q6. The regulation states that clinical investigators must provide sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements and promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study. If a clinical investigator provides updated information, does the applicant have to amend the application with updated financial disclosure information?

A. No. The applicant needs to report financial disclosure or certification only when the marketing application is submitted. However, under the regulation, investigators must promptly update their financial information whenever relevant changes occur during the course of the investigation and for 1 year following completion of the study. Sponsors and applicants are required to keep updated financial information from clinical investigators in company files.

Q7. 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. Yes, this may be acceptable. 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, then it would not be necessary to include a Form FDA 3455.

Q8. 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.

Q9. What does the applicant have to submit for investigators who did not provide financial disclosure information to the applicant?

A. If the applicant was unable to obtain some or all of the financial information needed to disclose or certify for a clinical investigator, the applicant must identify any disclosable financial interests or arrangements of which it is aware, certify that it acted with due diligence to obtain the information (listed as option 3 on Form FDA 3454), and include an attachment identifying the reason why any missing information could not be obtained.

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.

Q10. 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.

Q11. 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.