



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-D-5961]

In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies, and Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications; Draft Guidances for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of two draft guidances for industry entitled “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” (in vitro DDI guidance) and “Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications” (clinical DDI guidance).

These two draft guidances will update and replace the revised draft guidance for industry entitled “Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” issued February 21, 2012 (2012 draft guidance). These draft guidances are intended to assist drug developers in the planning and evaluation of drug-drug interaction (DDI) potential during drug development. In particular, the in vitro DDI guidance focuses on in vitro experimental approaches for evaluating metabolizing enzyme- and transporter-based drug interaction potential and how to extrapolate in vitro data to decide on the need for clinical DDI studies. The clinical DDI guidance focuses on clinical studies that evaluate the potential for DDIs, which alter a drug’s pharmacokinetics by modulating the effects of drug metabolizing enzymes and transporters, and advises sponsors on the timing and design of the clinical studies,

interpretation of the results, and options for managing DDIs in patients. Together, these two draft guidances describe a systematic, risk-based approach to the assessment of DDIs.

DATES: Submit either electronic or written comments on these draft guidances by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on these two draft guidances before it begins work on the final versions of these guidances.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2017-D-5961 for “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies, and Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications; Draft Guidances for Industry; Availability.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets

Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.”

Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidances to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance documents.

FOR FURTHER INFORMATION CONTACT: Lauren Brum, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3188, Silver Spring, MD 20903-0002, 301-796-5008, or OCP@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of two draft guidances for industry entitled “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” and “Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications.” The concomitant use of more than one medication in a patient is common. Unanticipated, unrecognized, or mismanaged DDIs are an important cause of morbidity and mortality associated with prescription drug use and has occasionally been the basis for withdrawal of approved drugs from the market. In some instances, understanding how to safely manage a DDI can allow approval of a drug that would otherwise have an unacceptable level of risk. Clinically relevant DDIs between an investigational drug and other drugs should therefore: (1) be defined during drug development as part of an adequate assessment of the drug’s overall benefit/risk profile; (2) be known at the time of the drug’s approval; and (3) be communicated in labeling. These two draft guidances are intended to assist drug developers in the planning and evaluation of DDI potential during drug development. In particular, the in vitro DDI guidance focuses on in vitro experimental approaches for evaluating metabolizing enzyme- and transporter-based drug interaction potential, and how to extrapolate in vitro data to decide on the need for clinical DDI studies. The appendix of the in vitro DDI guidance includes considerations in the choice of in vitro experimental systems, key issues regarding in vitro experimental conditions, and a more detailed explanation of model-based DDI prediction strategies. If in vitro assessments indicate the need to conduct clinical DDI studies, sponsors should consult the related clinical DDI guidance. The clinical DDI guidance focuses on clinical studies that evaluate DDIs that alter a drug’s pharmacokinetics by modulating the effects of drug metabolizing enzymes and/or

transporters and advises sponsors on the timing and design of the clinical studies, interpretation of the results, and options for DDI management in patients. Together, the two draft guidances describe a systematic, risk-based approach to evaluation and communication of DDIs.

In the *Federal Register* of February 21, 2012 (77 FR 9946), FDA announced the availability of a revised draft guidance entitled “Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.” We received comments on the 2012 draft guidance and have considered these comments while updating the information in the two draft guidances. In addition, new developments in the field have been incorporated to reflect the Agency’s current thinking.

The Agency decided to divide the 2012 draft guidance into two guidances with one focusing on in vitro DDI evaluation and the other focusing on clinical DDI evaluation. We are publishing the two draft guidances to collect additional public comments. These new draft guidances focus on metabolism- and transporter-based drug interactions. Other types of interactions, e.g., drug-therapeutic protein interactions and pH-dependent drug interactions, are not included. Separate guidances will be developed to cover other types of DDIs. In addition, a draft guidance specific to Section 7 (Drug Interactions) labeling will be developed to delineate the communication of DDI information in labeling.

These two draft guidances are being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). These draft guidances, when finalized, will represent the Agency’s current thinking on “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” and “Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications.” It does not establish any rights for any person and is not binding on FDA

or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. These guidances are not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

These draft guidances refer to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR 314.50(d) have been approved under OMB control number 0910-0001.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <https://www.regulations.gov>.

Dated: October 19, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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