

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-1415]

Framework for Assessment of Drug-Drug Interactions for Therapeutic Proteins; Establishment of a Public Docket; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for information and comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is establishing a public docket to assist with its development of a policy/guidance document on the assessment of drug-drug interactions (DDIs) for therapeutic proteins (TPs). The Agency split the 2012 DDI draft guidance into two draft guidance documents published in October 2017: “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” and “Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications.” The two guidance documents focus on enzyme- and transporter-based DDIs and do not include a discussion on TPs, which was originally included in the 2012 guidance. The Agency is currently revisiting the framework for assessment of DDIs for TPs outlined in the draft 2012 DDI guidance to offer timely and actionable information pertaining to DDIs for TPs and is seeking public input to assist in updating or creating a new framework.

DATES: Although you can comment at any time, to ensure that the Agency considers your comment in our development of recommendations, submit either electronic or written information and comments by July 9, 2018.

ADDRESSES: You may submit comments 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-2018-N-1415 for “Framework for Assessment of Drug-Drug Interactions for Therapeutic Proteins.” 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.

FOR FURTHER INFORMATION CONTACT:

Regarding human prescription drugs: Julie Chronis, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3203, Silver Spring, MD 20993-0002, 301-796-1200.

Regarding human prescription biological products: Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

Concurrent use of more than one prescription drug is common. A Centers for Disease Control and Prevention survey reports that about 20 percent of U.S. adults take three or more prescription drugs; and among adults age 65 and older, 40 percent take five or more medications.¹ Taking more than one drug at a time can result in DDIs which can result in toxicities or loss of efficacy. It is impractical to evaluate the impact of every possible drug combination. Therefore, the FDA

¹ Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey: [https://www.cdc.gov/nchs/data/16.pdf#079](https://www.cdc.gov/nchs/data/hus/16.pdf#079).

follows a systematic risk-based approach for DDI assessment.

Two draft guidance documents, when finalized, which are intended to assist drug developers in the planning and evaluation of the DDI potential of their drug during development were published in October 2017 entitled “Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications,” and “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies.”² These two draft guidances replaced the 2012 draft guidance entitled “Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.” The 2017 draft guidance documents focus on enzyme- and transporter-based DDIs; however, they do not discuss TPs.

The 2012 guidance recommended DDI assessment for TPs in three scenarios: (1) For cytokine or cytokine modulators, (2) for a known or suspected mechanism of DDI not related to effects on Cytochrome P450 enzymes or transporters, and (3) for when a TP is used in combination with another drug. The Agency now plans to revisit the previous framework for the assessment of DDIs for TPs that was included in the 2012 draft guidance. We are seeking public input on the revision and development of a framework to address DDIs for TPs with the goal of publishing this framework in a short policy/guidance document.

II. Additional Issues for Consideration and Request for Information

Interested persons are invited to provide detailed information and comments on the approach to the DDI assessment of TPs. Please read the information above regarding the submission of comments and confidential information. FDA is particularly interested in responses to the following overarching questions:

1. In what scenarios/circumstances and for which classes of TPs should DDI assessment be performed? Please provide rationale for your suggestions including available data and scientific principles to inform the considerations.

² “Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications” can be found at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>; provide comments to this guidance using docket number FDA-2017-D-596.

“In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” can be found at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>; provide comments to this guidance using docket number FDA-2017-D-5961.

2. For circumstances when DDI assessments are necessary:

a. What types of assessments can be useful (e.g., in vitro studies, dedicated clinical studies, population pharmacokinetic analyses, physiologically based pharmacokinetic analyses)? Please discuss the challenges and limitations with each type of assessment, and, as necessary, organize any discussions by the class of TP.

b. What are the study design considerations (e.g., population, analytes) for the types of assessments discussed in bullet 2a. above? Please describe the rationale for any design considerations proposed.

FDA will consider all information and comments submitted.

Dated: May 4, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-2513]

S3A Guidance: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies: Focus on Microsampling—Questions and Answers; International Council for Harmonisation; Guidance 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 a guidance entitled “S3A Guidance: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies: Focus on Microsampling—Questions and Answers.” The guidance was prepared under the auspices of the International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation. This question-and-answer (Q&A) guidance provides additional information to facilitate interpretation of the guideline for industry “S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies” (S3A guidance), especially to address the benefit and use of microsampling techniques in main study animals. The Q&A guidance is intended to provide points to consider before incorporating the microsampling

method in toxicokinetic studies and acknowledges the benefits (and some limitations) of the use of microsampling.

DATES: The announcement of the guidance is published in the **Federal Register** on May 10, 2018.

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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”).

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- 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-2016-D-2513 for “S3A Guidance: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies: Focus on Microsampling—Questions and Answers.” Received comments will be placed in the docket and, except for those submitted as “Confidential