4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-1820]

Framework for Assessing pH-Dependent Drug-Drug Interactions; Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, HHS.

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

SUMMARY: The Food and Drug Administration (FDA) is establishing a public docket to assist with the development of a policy or guidance document on the assessment of pH-dependent drug-drug interactions (DDIs). In October 2017, FDA published two draft guidance documents on DDIs entitled "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" (In Vitro Studies Draft Guidance) and "Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications" (Clinical Drug Interaction Studies Draft Guidance). These two draft guidances focus on enzyme- and transporter-based DDIs and do not include a framework to assess pH-dependent DDIs. FDA is seeking public input on best practices in the planning and evaluation of pH-dependent DDIs.

DATES: Submit either electronic or written comments on this notice by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments

until midnight Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

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-1820 for "Framework for Assessing pH-dependent Drug-Drug Interactions; Establishment of Public Docket; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), 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: Xinning Yang, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-7412, Xinning.Yang@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is establishing a public docket to assist with the development of a policy or guidance document on the assessment of pH-dependent DDIs. In October 2017, FDA published the In Vitro Studies draft guidance and the Clinical Drug Interaction Studies draft guidance (Refs. 1 and 2). These draft guidance documents assist drug developers in the planning and evaluation of DDI studies during drug development. These draft guidance documents also focus

on enzyme- and transporter-based DDIs but do not include a framework for assessing DDIs caused by drug-induced changes in gastric pH.

Acid-reducing agents (ARAs) such as antacids, histamine H_2-receptor antagonists (H_2 blockers), and proton pump inhibitors (PPIs) are widely used, and many of these products are available over the counter (Refs. 3 and 4). For a drug whose solubility is pH-dependent, concomitant administration with an ARA may affect its absorption and systemic exposure, potentially resulting in loss of efficacy or, in some cases, increased toxicity. Therefore, it is important to assess a drug's susceptibility to pH-dependent DDIs during drug development, characterize the DDI effect with clinical studies when needed, and communicate study results in the drug labeling (Ref. 4). FDA is seeking public input to inform a framework to assess pH-dependent DDIs.

II. Request for Information and Comments

Interested persons are invited to provide detailed information and comments on approaches to assess pH-dependent DDIs. You may also submit information and comments in a confidential manner (see *Instructions* in the ADDRESSES section). FDA is particularly interested in responses to the following overarching questions:

1. What are the characteristics of drugs that are susceptible to pH-dependent DDIs? Can a stepwise approach be applied to evaluate the interaction potential? Please provide the rationale for your suggestions.
2. When conducting pH-dependent DDI assessments:
    a. What are the utilities and limitations of different approaches to evaluating DDIs (e.g., in silico, in vitro, and dedicated clinical studies, as well as population pharmacokinetic analyses)?

b. What are the study design considerations (e.g., study population, choice of ARAs, dosing regimen and administration, and pharmacokinetic sampling) for the in vivo assessments discussed in 2a above? Please describe the rationale for any design considerations proposed.

c. Can we extrapolate the findings from a clinical DDI study with one ARA drug (a PPI, H_2 blocker, or antacid) to anticipate the DDI potential for other ARAs in the same class or in a different class? Please provide the rationale for your proposal.

FDA will consider all information and comments submitted in a timely manner (see ADDRESSES).

III. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA Draft Guidance for Industry, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies," October 2017. Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf.

2. FDA Draft Guidance for Industry, "Clinical Drug Interaction Studies--Study Design, Data Analysis, and Clinical Implications," October 2017. Available at https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf.

3. Centers for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Survey. Available at https://www.cdc.gov/nchs/data/hus/hus16.pdf#079 (accessed May 16, 2018).

4. Zhang, L., F. Wu, S. C. Lee, et al., "pH-Dependent Drug-Drug Interactions for Weak Base Drugs: Potential Implications for New Drug Development," *Clinical Pharmacology and Therapeutics*, 96(2):266-277, 2014.

Dated: May 17, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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