

and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:**

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**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 In October 2017, FDA published the In Vitro Studies draft guidance and the Clinical Drug Interaction Studies draft guidance (Refs. 1 and 2). These draft guidance documents assist drug developers in the planning and evaluation of DDI studies during drug development. These draft guidance documents also focus on enzyme- and transporter-based DDIs but do not include a framework for assessing DDIs caused by drug-induced changes in gastric pH.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<sub>2</sub>-receptor antagonists (H<sub>2</sub> 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<sub>2</sub> 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/Guidance/ComplianceRegulatoryInformation/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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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA–2005–D–0461]

**Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment; 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 for industry entitled "Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment." This guidance provides recommendations to industry for establishing the clinical effectiveness of drugs for the treatment of acne vulgaris (acne). This guidance finalizes the draft guidance for industry entitled "Acne Vulgaris: Developing Drugs for Treatment," issued September 19, 2005.

**DATES:** The announcement of the guidance is published in the **Federal Register** on May 22, 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”).

#### 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-2005-D-0461 for “Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment; Guidance for Industry.” 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 this guidance 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 guidance document.

#### FOR FURTHER INFORMATION CONTACT:

Strother D. Dixon, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5168, Silver Spring, MD 20993-0002, 301-796-1015.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of a guidance for industry entitled “Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment.” This guidance provides recommendations to industry for establishing the clinical effectiveness of drugs for the treatment of acne. This guidance finalizes the draft guidance for industry entitled “Acne Vulgaris: Developing Drugs for Treatment,” issued September 19, 2005 (70 FR 54945). Comments on the draft guidance were considered while finalizing this guidance. Changes made to the draft guidance include reformatting into a bulleted presentation and streamlining of information to core recommendations.

This guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on establishing the effectiveness of drugs intended to treat acne. 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. This guidance is not subject to Executive Order 12866.

##### II. Electronic Access

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

Dated: May 17, 2018.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2013-D-1020]

#### Bioanalytical Method Validation; 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 final guidance for industry entitled “Bioanalytical Method Validation.” This final guidance incorporates public comments to the revised draft published in 2013 as well as the latest scientific feedback concerning bioanalytical method validation and provides the most up-to-date information needed by drug developers to ensure the bioanalytical quality of their data.

**DATES:** The announcement of the guidance is published in the **Federal Register** on May 22, 2018.

**ADDRESSES:** You may submit either electronic or written comments on Agency guidances at any time as follows:

#### Electronic Submissions

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• *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