4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-D-1517]

The Use of Physiologically Based Pharmacokinetic Analyses--Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "The Use of Physiologically Based Pharmacokinetic Analyses--Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls." This guidance provides general recommendations regarding the development, evaluation, and use of physiologically based pharmacokinetic (PBPK) analyses for biopharmaceutics applications employed by sponsors of investigational new drug applications, new drug applications, or abbreviated new drug applications, and supplements to these applications, for oral drug product development, manufacturing changes, and controls. The guidance covers how to develop, evaluate, and apply PBPK models for biopharmaceutics-related uses, such as establishing clinically relevant dissolution specifications and quality risk assessment for postapproval manufacturing changes.

DATES: Submit either electronic or written comments on the draft guidance by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to ensure that the Agency

considers your comment on this draft guidance before it begins work on the final version of the guidance.

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-2020-D-1517] for "The Use of Physiologically Based Pharmacokinetic Analyses--Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls." 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, 240-402-7500.

- 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.govinfo.gov/content/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, 240-402-7500.

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 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 draft guidance document.

FOR FURTHER INFORMATION CONTACT: Paul Seo, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 1628, Silver Spring, MD 20993-0002, 301-796-4874.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "The Use of Physiologically Based Pharmacokinetic Analyses--Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls." This draft guidance provides general recommendations regarding the development, evaluation, and use of PBPK analyses for biopharmaceutics applications employed by sponsors of investigational new drug applications, new drug applications, or abbreviated new drug applications, and supplements to these applications, for oral drug product development, manufacturing changes, and controls. PBPK analyses use models and simulations that combine physiology, population, and drug characteristics to mechanistically describe the pharmacokinetic and/or pharmacodynamic behaviors of a drug product.

Submission of these analyses to FDA is discussed in the guidance for industry entitled "Physiologically Based Pharmacokinetic Analyses--Format and Content" (available at https://www.fda.gov/media/101469/download). However, the application of PBPK modeling in support of drug product development is an evolving field. FDA recognizes this challenge and encourages the development and use of new tools and approaches for linking pharmaceutical quality to clinical performance.

Advances in modeling and simulation have enabled the integration of factors such as the physicochemical properties of the active pharmaceutical ingredient, dissolution data, and the physiology of the gastrointestinal tract into the development of PBPK models. As such, PBPK modeling has become a promising tool in predicting systemic drug exposure of oral drug products.

PBPK analyses for biopharmaceutics applications combine dissolution modeling, biopredictive dissolution profiles, or other in vitro testing inputs with PBPK modeling strategies to quantitatively describe the differential and potential interactions of formulation variants with the body and their effect on drug exposure.

This guidance describes recommended PBPK model structure, which provides a mechanistic framework of drug oral absorption by representing the in vivo drug absorption process and accounting for the relevant product quality attributes that affect drug dissolution and absorption, and discusses how to capture and present model assumptions and parameters. Model validation and refinement are also discussed.

In addition, the guidance discusses the major regulatory uses of PBPK modeling for biopharmaceutics applications with respect to supporting product quality. Factors regarding the development of clinically relevant dissolution specifications to aid in biopredictive dissolution method development and to support clinically relevant dissolution acceptance criteria are presented, as well as considerations for conducting virtual bioequivalence studies.

PBPK modeling for biopharmaceutics applications also can be used to establish clinically relevant drug product quality specifications other than dissolution, which can be used to ensure bioequivalence of batches within the specification limits, to the pivotal clinical/bioavailability batches, or to the reference listed drug for generic drugs. Finally, the guidance discusses the use of PBPK analyses for biopharmaceutics applications as an advanced tool for quality risk assessment and management in both the pre- and postapproval stages.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current

thinking of FDA on "The Use of Physiologically Based Pharmacokinetic Analyses--Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls." 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.

II. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved FDA collections of information. 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. 3501-3521). The collections of information in 21 CFR part 314 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/guidance-compliance-regulatory-information/guidances-drugs or https://www.regulations.gov.

Dated: September 23, 2020.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2020-21652 Filed: 9/30/2020 8:45 am; Publication Date: 10/1/2020]