

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance for industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

In September 2020, the ICH Assembly endorsed the draft guidance entitled "Q3D(R2)—Guideline for Elemental Impurities" and agreed that the guidance should be made available for public comment. The draft guidance is the product of the Quality Expert Working Group of the ICH. Comments about this draft guidance will be considered by FDA and the Quality Expert Working Group.

The draft guidance provides guidance on PDEs for the cutaneous and transcutaneous routes of administration and relevant risk assessment considerations to supplement previous guidance for the oral, parenteral, and inhalation routes of administration. In addition, error corrections to previously identified PDEs for gold (oral, parenteral, and inhalation routes), silver (parenteral route), and nickel (inhalation route) are provided.

This draft guidance has been left in the original ICH format. The final guidance will be reformatted and edited to conform with FDA's good guidance practices regulation (21 CFR 10.115) and style before publication. The draft guidance, when finalized, will represent the current thinking of FDA on "Q3D(R2)—Guideline for Elemental Impurities." 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

FDA tentatively concludes that this draft guidance contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at <https://www.regulations.gov>, <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, or [https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-](https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances)

information-biologics/biologics-guidances.

Dated: May 7, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-3614]

M9 Biopharmaceutics Classification System-Based Biowaivers; 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 final guidance for industry entitled "M9 Biopharmaceutics Classification System-Based Biowaivers." The guidance was prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), formerly the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The guidance provides recommendations to support the biopharmaceutics classification of drug substances and the Biopharmaceutics Classification System (BCS)-based waiver of the in vivo bioequivalence (BE) study requirement for certain drug products. The guidance is intended to avoid or reduce the need for human BE trials based on extensive in vitro characterization of the drug substance and drug product properties. The guidance replaces the existing FDA guidance issued December 26, 2017, entitled "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System." The guidance also finalizes the draft ICH guidance, "M9 Biopharmaceutics Classification System-Based Biowaivers," issued on October 26, 2018.

DATES: The announcement of the guidance is published in the **Federal Register** on May 12, 2021.

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-2018-D-3614 for "M9 Biopharmaceutics Classification System-Based Biowaivers." 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 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, or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 240-402-8010. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Mehul Mehta,

Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2178, Silver Spring, MD 20993-0002, 301-796-1573; or 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.

Regarding the ICH: Jill Adleberg, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6364, Silver Spring, MD 20993-0002, 301-796-5259.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "M9 Biopharmaceutics Classification System-Based Biowaivers." The guidance was prepared under the auspices of ICH. ICH has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, high-quality medicines are developed, registered, and maintained in the most resource-efficient manner.

By harmonizing the regulatory requirements in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized the reporting of important safety information, standardized marketing application submissions, and made many other improvements in the quality of global drug development and manufacturing and the products available to patients.

The six Founding Members of the ICH are FDA; the Pharmaceutical Research and Manufacturers of America; the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; and the Japanese Pharmaceutical Manufacturers Association. The Standing Members of the ICH Association include Health Canada and Swissmedic. Additionally, the Membership of ICH has expanded to include other regulatory authorities and industry associations from around the world (refer to <https://www.ich.org/>).

ICH works by involving technical experts from both regulators and industry parties in detailed technical harmonization work and the application of a science-based approach to harmonization through a consensus-driven process that results in the development of ICH guidelines. The regulators around the world are

committed to consistently adopting these consensus-based guidelines, realizing the benefits for patients and for industry.

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance for industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

In the **Federal Register** of October 26, 2018 (83 FR 54107), FDA published a notice announcing the availability of a draft guidance entitled "M9 Biopharmaceutics Classification System-Based Biowaivers." The notice gave interested persons an opportunity to submit comments by January 24, 2019.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Assembly and endorsed by the regulatory agency members in November 2019.

The guidance provides recommendations to support the biopharmaceutics classification of drug substances and the BCS-based waiver of the in vivo BE study requirement for drug products. The BCS-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies. In vivo bioequivalence studies may be waived if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance or substances. The BCS categorizes drug substances into one of four BCS classes as follows:

- Class I: High solubility, high permeability
- Class II: Low solubility, high permeability
- Class III: High solubility, low permeability
- Class IV: Low solubility, low permeability

In vivo BE studies are needed to demonstrate lack of impact of significant formulation changes on a drug's bioavailability during its development, for post approval line extensions, and when developing a generic product. Utilizing the critical properties of the drug substance and the drug product, and applying the BCS framework, extensive in vitro studies

can support the waiver of the in vivo BE requirement for certain drug products.

Following the public consultation period, clarifications were made to the guidance based on the comments received.

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 "M9 Biopharmaceuticals Classification System-Based Biowaivers." 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

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521) is not required. However, this final guidance refers to previously approved FDA collections of information. The previously approved collections of information are subject to review by OMB under the PRA. The following collections of information have been approved under OMB control number 0910–0001:

- Submitting under 21 CFR 314.50 content and format of new drug applications, including the pharmacokinetics and bioavailability sections.
- Submitting under 21 CFR 314.70 postapproval changes.
- Submitting under 21 CFR 314.94 content and format of abbreviated new drug applications.

The collections of information for submitting under 21 CFR 312.23 information about pharmacokinetics and biological disposition of the drug has been approved under OMB control number 0910–0014.

III. Electronic Access

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

Dated: May 6, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–D–4524]

S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals; 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 final guidance for industry entitled “S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals.” The guidance was prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), formerly the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The guidance recommends international standards for the nonclinical safety studies recommended to support the development of pediatric medicines. The guidance provides a weight of evidence approach to determine when nonclinical toxicity studies may be recommended in juvenile animals. If such studies are recommended, the guidance provides appropriate study designs. The guidance is intended to promote harmonization of recommendations for such studies and should facilitate the timely conduct of pediatric clinical trials and reduce the use of animals in accordance with the 3R (replace/reduce/refine) principles. Tissue engineered products, gene and cellular therapies, and vaccines are excluded from the scope of this guidance. The guidance replaces the draft guidance issued on February 1, 2019.

DATES: The announcement of the guidance is published in the **Federal Register** on May 12, 2021.

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

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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>.

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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–2018–D–4524 for “S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals.” 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