4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No.FDA-2026-D-6539]

# Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a draft guidance for industry entitled "Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials." The guidance is intended to provide recommendations in the application of quantitative systems pharmacology (QSP) modeling when a minimum anticipated biological effect level (MABEL) in first-in-human (FIH), phase 1 trials for drugs and biological products is recommended. This guidance focuses on drugs and biological products for which the MABEL approach can be used to guide starting doses for FIH trials. This includes, but is not limited to, drugs and biological products that may cause cytokine release, T-cell activation, or other potent pharmacological reactions.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2026-D-6539 for "Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials." 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: Qi Liu, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993, Qi.Liu@fda.hhs.gov, 301–796–1568.

SUPPLEMENTARY INFORMATION:

## I. Background

Historically, FIH starting doses were often derived from animal toxicology studies and have been based on the highest non-adverse effect level observed in animals (NOAEL), highest severely toxic doses in 10% of rodents (STD10), or highest non-severely toxic doses in non-rodent species (HNSTD), converted to a human equivalent dose. Although these approaches have been appropriate for many drugs and biological products, there are limitations for certain high-risk products (e.g., immunostimulatory monoclonal antibodies). In response, the concept of MABEL was developed. MABEL is defined as a dose expected to produce a minimal biological effect in humans. Determining MABEL typically involves using pharmacologic activity and receptor binding data (human cell lines), while also integrating any other relevant data (e.g., animal safety and pharmacokinetic data), as appropriate, to predict a dose that is just at the onset of biological activity.

QSP has emerged as a tool to model disease progression and complex drug–biological system interactions. QSP merges an understanding of biological systems and a drug's exposure-response, enabling modeling and simulation of how a drug engages its target and triggers downstream biological responses in a mechanistic, quantitative manner. Over the past decade, there has been a notable increase in regulatory submissions (e.g., investigational new drug

applications (INDs), biologics license applications (BLAs), and new drug applications (NDAs)) that include QSP modeling to support various decisions, such as informing FIH dose selection, particularly for drugs and biological products where traditional methods may fall short. For example, certain drugs and biological products have highly specific targets that only exist in humans and can elicit steep pharmacodynamic responses (e.g., cytokine release or T-cell activation) that are difficult to predict from animal studies alone. In many cases, the relevant target may be absent or differently expressed in animal species, limiting the translational relevance of animal toxicity data. Standard allometric scaling of doses also might not account for such pharmacological differences. Therefore, a model-based approach that considers all available data (e.g., in vitro, in vivo, disease progression, clinical experience from compounds with both similar structure and similar mechanism of action, and in silico) may be more appropriate to estimate a starting dose in the FIH trial. In addition, QSP modeling may derive potential efficacy- and safety-related information and balance them in a quantitative manner to inform FIH dose selection. This guidance specifically addresses those needs by outlining how QSP models can be developed and used to estimate a MABEL for drugs and biological products entering FIH trials.

This 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 "Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials." 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.

As we develop final guidance on this topic, FDA will consider comments on costs or cost savings the guidance may generate, relevant for Executive Order 14192.

## II. Paperwork Reduction Act of 1995

While this guidance document contains no new collections of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 312, including the submission of rationale and dose determination, as set forth in part 312.23; the submission of detailed technical information, as set forth in part 312.31; and the submission of meeting requests and supporting documentation, as set forth in part 312.47, have been approved under OMB control number 0910-0014.

## III. Electronic Access

Persons with access to the internet may obtain the draft guidance at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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