DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2024–N–5975]

Use of a Type V Drug Master File for Model Master File Submissions To Support Abbreviated New Drug Applications; 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 or Agency), Center for Drug Evaluation and Research (CDER), Office of Generic Drugs is establishing a public docket entitled ''Use of a Type V Drug Master File (DMF) for Model Master File (MMF) Submissions to Support Abbreviated New Drug Applications (ANDAs).'' The purpose of this docket to solicit input from interested parties on this topic.

DATES: Submit either electronic or written comments on the notice by April 17, 2025 to ensure that the Agency considers your comment. The docket number is FDA–2024–N–5975.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time April 17, 2025. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received 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–2024–N–5975 for ''Use of a Type V Drug Master File for Model Master File Submissions to Support Abbreviated New Drug Applications; Establishment of a 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, 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.

FOR FURTHER INFORMATION CONTACT: Lanyan (Lucy) Fang, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 75, Rm. 4686, Silver Spring, MD 20993–0002, 301–796–5005, *mmf@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

Computational (in silico) modeling and simulation (M&S) is a regulatory science priority at FDA given the rapid growth in drug developers' use of data science and model-based technologies. An example is the increasing use of quantitative methods and modeling (QMM) and simulation approaches by the generic drug industry and regulatory agencies, including FDA, to support generic product development and ANDA regulatory assessments.[1] These QMM approaches generally involve mechanistic modeling such as physiologically based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD) modeling, quantitative clinical pharmacology tool sets such as population pharmacokinetics (PPK) approaches, and advanced data analytics methodologies. Generic drug developers are utilizing QMM and simulation approaches to generate MIE to, for example, support alternative BE approaches and to minimize the burden

[1] See, *e.g.,* guidance for industry ''Physiologically Based Pharmacokinetic Analyses—Format and Content'' (August 2018); see also, draft guidance for industry ''The Use of Physiologically Based Pharmacokinetic Analyses—Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls'' (October 2020). When final, this guidance will represent the FDA's current thinking on this topic. FDA updates guidances periodically; the most recent version of a guidance can be found at FDA's Drugs guidance web page at *https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

of, or even eliminate the need for, in vivo studies to establish BE.

While QMM approaches that generate MIE provide significant value to the development, review, and approval of high-quality generic drugs, these frameworks are evolving amidst challenges and complications facing industry that are incidental to the growing use of new and complex modeling technologies. For example, the data and information needed to verify and validate a model may not be available to the general public (*e.g.,* proprietary), or if publicly available, insufficient, and generating original data for model verification and validation (V&V) can be a time-consuming and costly investment. At the same time, certain M&S approaches may provide an opportunity for certain models, once they are supported by sufficient V&V, to be viewed as shareable across different products and formulations and utilized by multiple ANDA applicants for the same context of use. For purposes of this notice, an ''MMF'' or ''MMF submission'' refers to a set of information and data on an in silico quantitative model or modeling platform supported by sufficient V&V. MMFs can be established to support MIE in a broad range of quantitative models, including, but not limited to, PBPK, CFD, PPK, and mechanistic in vitro in vivo correlation models. There are different types of MMFs, including, but not limited to, drug product-specific models, a verified and validated in silico framework for products following the same route of administration, and a recognized modeling methodology or framework for a particular context of use (Ref. 1).

FDA recognizes the evolving role MIE plays in generic drug development and other regulatory applications, as well as industry's corollary desire for an improved framework for in silico model-sharing, model acceptance, and related communication with and submission to FDA. Use of the Type V DMF to efficiently leverage MMFs within the scope of successful MIE approaches may help advance generic drug development and facilitate the ANDA review and approval processes.

A DMF is a voluntary submission that may be used to provide confidential detailed information to the Agency (Ref. 2). A DMF is submitted solely at the discretion of the DMF holder. There are several types of DMFs; a Type V is used for ''FDA-accepted reference information.'' (§ 314.420(a)(5) (21 CFR 314.420(a)(5))). The use of a DMF is not a requirement for the submission of MMFs to the Agency; however, the holder of a Type V DMF can authorize one or more ANDA applicants to incorporate by reference information and data contained in the DMF without having to disclose that information and data to the applicant(s). When authorized by the DMF holder, ANDA applicants can use information and data contained in the DMF to support, but not substitute for, their ANDA submissions. A DMF is neither approved nor disapproved. Its technical content (in this case, the MMF) is typically reviewed by FDA only in connection with the review of a premarket application (Ref. 2 at 6). A Type V DMF, including a Type V DMF for MMF submissions to support an ANDA, may be submitted on an ongoing basis.

Prospective DMF holders who are interested in using a Type V DMF, including a Type V DMF for MMF submissions to support ANDAs, must first email a letter of intent to the DMF staff (see Ref. 2 at 16 (citing § 314.420(a)(5))). The draft guidance for industry ''Drug Master Files'' provides detailed information about preparing and submitting DMFs and FDA's DMF review process, including that an emailed letter of intent should be sent to (*dmfquestion@fda.hhs.gov*) and include a clearly stated subject field and other necessary information (Ref. 2 at 16). For example, applicants that have submitted a Type V DMF for MMF submissions to support ANDAs have submitted the letter of intent with a subject field, such as ''Letter of Intent to Submit Type V DMF for MMF Submission to Support ANDAs''. For more information on submitting Type V DMFs, see FDA's DMF web page and the FDA Guidance for Industry ''Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications'' (Ref. 3).[2]

II. Request for Comments

FDA is opening a docket to solicit feedback from the public on the use of a Type V DMF for MMF submissions to support ANDAs. FDA welcomes any relevant information that interested parties and other members of the public wish to share. At the close of the comment period, the Agency will collect this feedback for consideration.

III. References

The following references marked with an asterisk (*) are on display at 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 also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. Although 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. Fang, L., Y. Gong, A.C. Hooker, et al., 2024, ''The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA,'' *The AAPS Journal,* 26(2):28–35 available at 10.1208/s12248–024–00897–8.

* 2. FDA Draft Guidance for Industry ''Drug Master Files,'' October 2019: *https://www.fda.gov/media/131861/download.*

* 3. FDA Guidance for Industry ''Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications,'' September 2024, Rev. 8: *https://www.fda.gov/media/135373/download.*

Dated: January 14, 2025.

P. Ritu Nalubola,

Associate Commissioner for Policy.

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[2] See also, FDA's DMF web page, available at *https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2024–D–5663]

Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy: Developing Drug and Biological Products in Oncology; 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 ''Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy: Developing Drug and Biological Products in Oncology.'' Chemotherapy-induced peripheral neuropathy (CIPN), a painful, disabling, and potentially irreversible condition commonly affecting patients receiving neurotoxic chemotherapies, could diminish survival by potentially increasing chemotherapy treatment interruptions, dose reductions, and discontinuations. This guidance