



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2026-N-0809]

Recommendations on Scale-Up and Postapproval Changes Guidances for Industry; Request for Comments.

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for information and comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing the opening of a public docket to solicit information and comments on the Agency's series of guidances for industry on scale-up and postapproval changes (SUPAC) for specific dosage forms. Specifically, we are seeking comment on the following guidances for industry:

“Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation” (SUPAC-IR); “SUPAC-IR Questions and Answers about SUPAC-IR Guidance” (SUPAC-IR Q&A); “Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation” (SUPAC-SS); “SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation” (SUPAC-MR); and “SUPAC: Manufacturing Equipment Addendum” (SUPAC-MEA). The Agency is seeking public information and comment on the continued utility of and suggestions for potential revisions to the recommendations in these guidances.

DATES: Submit either electronic or written comments on the notice by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the

Agency considers your comment on these guidance documents before it begins work on any revisions.

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 at the end of [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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-2026-N-0809] for "Recommendations on Scale-Up and Postapproval Changes Guidances for Industry; 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: Ashley Boam, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4192, Silver Spring, MD 20993-0002, 301-796-6341, cder-quality-policy@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

After a series of workshops with interested partners and FDA-sponsored research in the 1990s, FDA's Center for Drug Evaluation and Research developed a risk-based approach for implementing chemistry, manufacturing, and controls (CMC) changes that could affect identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. This risk-based approach was first explained in the SUPAC guidances, which describe the recommended testing and documentation for component and composition changes, manufacturing process and equipment changes, manufacturing scale changes, and manufacturing site changes. The intent of this risk-based approach was to reduce the regulatory burden of obtaining FDA approval for certain CMC changes to approved applications that were not likely to affect the identity, strength, quality, purity, or potency of a drug product and, therefore, the safety or effectiveness of the drug product.

In November 1997, the risk-based approach for implementing CMC changes that was introduced in the SUPAC guidances was codified in section 116 of the Food and Drug Administration Modernization Act (FDAMA) (Pub. L. 105-115). Section 116 of FDAMA

amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) by adding section 506A (21 U.S.C. 356a), which describes requirements and procedures for making and reporting any CMC changes to approved applications, including new and abbreviated new drug applications. On April 8, 2004, FDA issued the final rule to implement section 506A of the FD&C Act (69 FR 18728). The final rule requires applicants to assess the effects of CMC changes on the identity, strength, quality, purity, and potency of a drug product as they may relate to the safety and effectiveness of the product. Further, the final rule sets forth submission requirements, based on the characterization of the CMC change (e.g., major, moderate, or minor), that must be met before the distribution of the product made using the change (see 21 CFR 314.70). In the preamble to the final rule, FDA acknowledged that when section 116 of FDAMA was written it was anticipated that “the science of manufacturing would evolve over time,” and that “FDA may, by regulation or guidance, change the designation of a particular category of change from major to nonmajor or vice versa” (69 FR 18728 at 18729). The final rule was effective on June 22, 2004.

Except for SUPAC-MEA, which was updated in 2014, the SUPAC guidances were finalized between 1995 and 1997. Since then, the use and evolution of risk assessment tools in pharmaceutical development has enhanced the ability to identify, categorize, and control risks associated with a CMC change that impact product quality. We have determined that the SUPAC guidances may benefit from additional public comment on the topics outlined in this notice to ensure that these guidances align with current expectations, risk assessment strategies, and contemporary scientific and technical considerations.

II. Issues for Consideration and Requested Information and Comments

Despite the time that has elapsed since the SUPAC guidances were implemented, the core principle of a risk-based approach for implementing CMC changes as described in the guidances remains relevant. The SUPAC guidances assist in reducing the number of CMC changes that require approval of a supplemental application, which can minimize delays in distribution of the

product, give companies greater control over their production resources, and result in significant net savings to industry. In addition, the SUPAC guidances allow FDA to focus resources on those changes that pose the greatest risk to product quality thereby improving efficiency and promoting timely continual improvement in accordance with current good manufacturing practice. We acknowledge, however, that the effectiveness of the SUPAC guidances may be impacted by subsequent guidances (e.g., ICH Q9(R1) and ICH Q12)), where particular recommendations in those guidances either supersede or potentially conflict with certain recommendations in the SUPAC guidances. For example, the principles described in ICH Q12 (e.g., how enhanced development can inform the nature and extent of established conditions, further elaboration on change management as an aspect of the pharmaceutical quality system) are intended to enhance industry's ability to manage many CMC changes with greater efficiency and with less regulatory oversight prior to implementation of the change. Accordingly, FDA is considering updating the SUPAC guidances to improve their utility and effectiveness in light of evolving science, to ensure they continue to reflect the Agency's current thinking on risk-based approaches to CMC changes, and to enable manufacturers to more effectively evaluate changes within their quality systems prior to submitting a CMC change for evaluation.

Interested persons are invited to provide detailed comments and information related to the contents of this notice. To facilitate input, we have developed the following questions about the SUPAC guidances:

1. How are the recommendations provided in the SUPAC guidances still helpful and meaningful to regulated industry?
 - a. Are there sections of the SUPAC guidances that are particularly beneficial and are important to retain, either partially or in their entirety, because they reflect current risk-based approaches and are currently being referenced by applicants to support CMC changes?

- b. Are the risk-based principles described in the SUPAC guidances being used to help inform applicants in other ways in addition to supporting CMC changes?
 2. What challenges do you have when interpreting or applying the recommendations in the SUPAC guidances?
 - a. Are there sections of the SUPAC guidances that should be removed because they are no longer relevant or meaningful?
 - b. When referencing the SUPAC guidances for recommendations on a CMC change, are you able to effectively evaluate changes within your quality system and readily identify both the type and the corresponding level of change (i.e., major, moderate, or minor) based on the information provided in the SUPAC guidances? If not, please specify what challenges you have when making this determination.
 - c. Are there areas of overlap or inconsistencies among the various SUPAC guidances or in other FDA guidances on CMC changes that may cause confusion when trying to apply the recommendations? Please specify the areas of overlap or inconsistencies.
 3. How can FDA provide clarity on the recommendations provided in the SUPAC guidances? For example:
 - a. Should FDA consider reorganizing the content in the SUPAC guidances, for example, by either combining the multiple SUPAC guidances into a single guidance, or separating topics in the individual guidances, so that recommendations are easier to interpret and apply?
 - b. Are there recommendations from other FDA guidances, for example, the studies described in the draft guidance for industry titled “Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in

ANDAs” (87 FR 64230),¹ that if included in the SUPAC guidances, might help to reduce regulatory burden?

- c. How might the recommendations in the SUPAC guidances be better aligned with current risk assessment and postapproval lifecycle management principles and tools (e.g., postapproval change management protocols, established conditions)?

4. Are there new topics that should be added to the SUPAC guidances?

These questions are not meant to be exhaustive, and we are also interested in any other pertinent information interested persons would like to share on this topic. This feedback will help inform the Agency's general policy development direction. FDA encourages commenters to provide the specific rationale and basis for their comments, including any available supporting data and information.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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¹ When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.