**4164-01-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2019-D-0298]**

# Quality Considerations for Continuous Manufacturing; Draft Guidance for Industry; Availability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**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Quality Considerations for Continuous Manufacturing." This draft guidance provides information regarding FDA's current thinking on the quality considerations for continuous manufacturing of small molecule, solid oral drug products that are regulated by the Center for Drug Evaluation and Research (CDER). The draft guidance describes several key quality considerations and provides recommendations for how applicants should address these considerations in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental NDAs and ANDAs, for small molecule, solid oral drug products that are produced via a continuous manufacturing process. FDA supports the development and implementation of continuous manufacturing for drug substances and all finished dosage forms where appropriate, including those submitted in NDAs, ANDAs, drug master files, biologics license applications (BLAs), and nonapplication over the counter products. Scientific principles described in this draft guidance may also be applicable to continuous manufacturing technologies used for these drugs. However, this draft guidance is not

intended to provide recommendations specific to continuous manufacturing technologies used for biological products under a BLA.

**DATES:** Submit either electronic or written comments on the draft guidance by **[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2019-D-0298 for "Quality Considerations for Continuous Manufacturing." 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.

- 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.gpo.gov/fdsys/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.

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:** Sau L. Lee, Center for Drug Evaluation and Research, Food and Drug Administration (HFD-600), 10903 New Hampshire Ave., Bldg. 22, Rm. 2130, Silver Spring, MD 20993-0002, 301-796-2905.

**SUPPLEMENTARY INFORMATION:**

## I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Quality Considerations for Continuous Manufacturing." The draft guidance was prepared by CDER's Office of Pharmaceutical Quality, which is committed to supporting and enabling pharmaceutical innovation and modernization as part of the Agency's mission to protect and promote public health. While the implementation of emerging technology, such as continuous manufacturing, is critical to modernizing pharmaceutical manufacturing and improving quality, FDA also recognizes that innovative approaches to manufacturing may represent challenges to industry and regulators. By the very nature of an approach being innovative, a limited knowledge and experiential base about the technology may exist. Pharmaceutical companies may have concerns that using continuous manufacturing could result in delays while FDA reviewers and investigators familiarize themselves with the new technologies and determine how they fit within existing regulatory approaches.

This draft guidance provides information regarding FDA's current thinking on the quality considerations for continuous manufacturing of small molecule, solid oral drug products that are regulated by CDER. The draft guidance describes several key quality considerations and provides recommendations for how applicants should address these considerations in NDAs, ANDAs, and supplemental NDAs and ANDAs, for small molecule, solid oral drug products that are produced via a continuous manufacturing process.

The draft guidance takes into account the comments that were submitted to Docket No. FDA-2017-N-2697 ("Submission of Proposed Recommendations for Industry on Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing; Establishment of Public Docket"). FDA invites general comments on the quality considerations described in the draft guidance, including comments on control strategy, facility, and process

validation considerations for continuous manufacturing of small molecule, solid oral drug products.

In addition to this draft guidance, pharmaceutical manufacturers with product-specific continuous manufacturing questions may submit a proposal to the Emerging Technology program. Refer to FDA guidance for industry, "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization" (September 2017) at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm478821.pdf.

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 "Quality Considerations for Continuous Manufacturing." 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. This guidance is not subject to Executive Order 12866.

## II. Additional Issues for Consideration

In addition to comments on the draft guidance generally, FDA is requesting comments and related supporting information on the following topics: (1) data storage and handling from process analytical technology systems, (2) potential approaches for situations where direct attribute measurement is not possible (e.g., low-dose compounds), (3) contract manufacturers employing continuous manufacturing, (4) risk-based reporting of routine model maintenance and updates, and (5) statistical approaches using large samples (e.g., Large N). FDA is seeking public comment on topics for potential inclusion in the final guidance or additional guidance and any other alternative approaches.

## III. Paperwork Reduction Act of 1995

This draft guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collections of information in 21 CFR parts 210-211 have been approved under OMB control number 0910-0139. The submission of INDs under 21 CFR 312.23 is approved by OMB control number 0910-0014. The submission of BLAs under 21 CFR 601.2 and 601.12 is approved by OMB control number 0910-0338. The submission of NDAs and ANDAs under 21 CFR 314.50, 314.70, 314.71, 314.94, and 314.97 is approved by OMB control number 0910-0001. The information to be included in a meeting request for a product submitted in an IND, BLA, or NDA is approved by OMB control number 0910-0429 ("Guidance for Industry on Formal Meetings Between the FDA and Sponsors or Applicants" (December 2017)). Information to be included in a meeting request for a product submitted in an ANDA is approved by OMB control number 0910-0797 ("Guidance on Controlled Correspondence Related to Generic Drug Development" (December 2015)).

## IV. Electronic Access

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

Dated: February 22, 2019.

**Lowell J. Schiller,**

*Acting Associate Commissioner for Policy.*

[FR Doc. 2019-03413 Filed: 2/26/2019 8:45 am; Publication Date: 2/27/2019]