Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/CMC

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. 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. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to pharmaceutical companies interested in participating in a program involving the submission of chemistry, manufacturing, and controls (CMC) information containing emerging manufacturing[2] technology to FDA. The program is open to companies that intend the technology to be included as part of an investigational new drug application (IND) or original or supplemental new drug application (NDA), abbreviated new drug application (ANDA), or biologic license application (BLA) reviewed by the Center for Drug Evaluation and Research (CDER), and where that technology meets other criteria described in this guidance.

Issues in pharmaceutical manufacturing have the potential to significantly impact patient care in that failures in quality may result in product recalls and harm to patients. Additionally, failures in product or facility quality are a major factor leading to disruptions in manufacturing. Modernizing manufacturing technology may lead to a more robust manufacturing process with fewer interruptions in production, fewer product failures (before or after distribution), and greater assurance that the drug products manufactured in any given period of time will provide the expected clinical performance. For example, contemporary aseptic manufacturing facilities that are highly automated and use isolators and other modern separation technologies have the potential to decrease the risk of contamination from the processing line. Encouraging the development of emerging manufacturing technology may lead to improved manufacturing, and therefore improved product quality and availability throughout a product's lifecycle.

In this program, pharmaceutical companies can submit pre-submission questions and proposals about the use of specific emerging technology to a group within CDER (Emerging Technology Team – ETT). The ETT will work in partnership with relevant pharmaceutical quality offices and assume a leadership or co-leadership role for the cross-functional quality assessment team

[1] This guidance has been prepared by representatives from the Office of Pharmaceutical Quality and the Office of Compliance in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purpose of this guidance, the definition of manufacturing also includes testing, packaging and labeling operations, and quality control.

(including review and on-site Agency evaluation) for submissions involving emerging technology. The ETT will serve as the primary point of contact for companies that are interested in implementing emerging manufacturing technology in the manufacture of their drug products and for the relevant quality assessment team to:

(a) Answer sponsor/applicant questions about the information FDA expects to see in their submission;

(b) Identify and help facilitate regulatory review of a new manufacturing technology in accordance with existing legal and regulatory standards, guidance, and Agency policy related to quality assessment;

(c) Serve as the lead or co-lead on the quality assessment team, in partnership with relevant CDER pharmaceutical quality offices, to review and make the final quality recommendation regarding the potential approval of submissions in the program; and

(d) Identify and capture resolution to policy issues that may inform FDA approaches and recommendations regarding future submissions that involve the same technology.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

CDER is committed to supporting and enabling the modernization of pharmaceutical manufacturing as part of the Agency's mission to protect and promote the public health. These efforts also may be one long-term solution to avoid drug shortages, as noted in FDA's drug shortage strategic plan.[3] As part of its commitment to modernizing pharmaceutical manufacturing, in 2002, FDA launched an initiative entitled "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach," to encourage the implementation of a modern, risk-based pharmaceutical quality assessment system.[4] The initiative was published with several goals, including encouraging the early adoption of new technological advances by the pharmaceutical industry and ensuring that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science. In 2004, this was further described in an FDA guidance for industry entitled *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.[5] This guidance describes the concept that quality cannot

[3] See http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf.

[4] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm#_Toc84065754.

[5] See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070305.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA

be tested into products; in other words, it should be built-in or should be present by design. Quality is built into pharmaceutical products through a comprehensive understanding of the intended use of the product, the characteristics of the product, and the design of the product and manufacturing process using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product's lifecycle.

While the implementation of emerging technology is critical to modernizing pharmaceutical manufacturing and improving quality, FDA also recognizes that innovative approaches to manufacturing may represent challenges to industry and the Agency. 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 such technologies could result in delays while FDA reviewers familiarize themselves with the new technologies and determine how they fit within existing regulatory approaches. Through the ETT, FDA intends to encourage the adoption of innovative approaches to pharmaceutical manufacturing by leveraging existing resources within the Agency to facilitate the regulatory review of submissions to the Agency involving manufacturing technologies likely to improve product safety, identity, strength, quality, and purity.

III. DISCUSSION

As part of this program, FDA intends to provide for early engagement and additional meeting opportunities for the participants and FDA to discuss manufacturing design and development issues as well as recommendations for submission content related to the emerging technology. FDA intends to work with each participant on an individual basis, and expects that the process will include appropriate coordination with the quality assessment team (FDA staff involved in the review of the CMC sections of the application and evaluation of the manufacturing facilities). Based on experience gained during the program, FDA intends to develop guidance and standards, as necessary, on emerging technologies and approaches to enable the modernization of the pharmaceutical manufacturing base.

A. Scope

Acceptance of a request to participate in this CDER program will depend on the applicant's proposed plan for submission of an IND or original or supplemental ANDA, BLA, or NDA, based on the criteria described below. The planned submission should include one or more elements subject to quality assessment for which the Agency has limited review or inspection experience, where the technology has the potential to modernize the pharmaceutical manufacturing body of knowledge to support more robust, predictable, or cost-effective processes. Examples of such elements include an innovative or novel: (1) product manufacturing technology, such as the dosage form; (2) manufacturing process (e.g., design, scale-up, and/or commercial scale)*;* and/or (3) testing technology. Every effort will be made to ensure that many companies have the opportunity to participate and that a wide variety of novel manufacturing

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Drugs guidance Web page at
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

technologies are included in this program. This program only affects the quality section of the submission (CMC and facility-related information). Existing requirements related to the review and approval of a submission will not be waived, suspended, or modified for purposes of this program. Applicants must make the submission in accordance with 21 CFR parts 312, 314, 601, and other applicable standards.

B. Process

Interested parties planning to submit an IND or original or supplemental BLA or NDA as part of this CDER program should submit a written request for a Type C meeting as described in the guidance on *Formal Meetings Between the FDA and Sponsors or Applicant*.[6] The request should specify the meeting request as a "Type C meeting – request to participate in the ETT program." Interested parties planning to submit an ANDA should submit a pre-ANDA meeting request and specify the meeting request as a "Pre-ANDA meeting – request to participate in the ETT program." Either type of request should be submitted at least three months prior to the planned application (IND, ANDA, BLA, NDA) submission date. The meeting request and related questions should be submitted electronically to CDER-ETT@fda.hhs.gov. In addition to the items outlined in the referenced guidance, the request should also include the following items:

(1) A brief description of the proposed testing, process, and/or proposed technology;

(2) A brief explanation why the proposed testing, process, and/or technology are substantially novel and unique and should be considered under this program;

(3) A description of how the proposed testing and/or technology could modernize pharmaceutical manufacturing and thus improve product safety, identity, strength, quality, or purity;

(4) A summary of the development plan and any perceived roadblocks to implementation (e.g., technical or regulatory); and

(5) A timeline for a submission (IND, ANDA, BLA, NDA, original or supplemental).

The request document should generally not exceed five pages of narrative, including up to five figures or tables. Based on the availability of Agency resources, we expect to limit acceptance into the program to technologies that are likely to modernize pharmaceutical manufacturing in order to improve product safety, identity, strength, quality, or purity, and with which the Agency has limited prior experience and knowledge. FDA expects to notify companies of its decision regarding acceptance into the program in writing within 60 days of receipt of the request. Although incomplete and/or unclear requests will generally be denied, FDA may contact the applicant to request additional information. Once accepted into the program, the participant can

[6] See http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf.

engage with the ETT and CMC review team in accordance with existing meeting procedures and guidance(s)[7] based on the availability of Agency resources.

[7] See the guidances on *Formal Meetings Between the FDA and Sponsors or Applicants* (see information on "Type C" meetings) and *Controlled Correspondence Related to Generic Drug Development*.