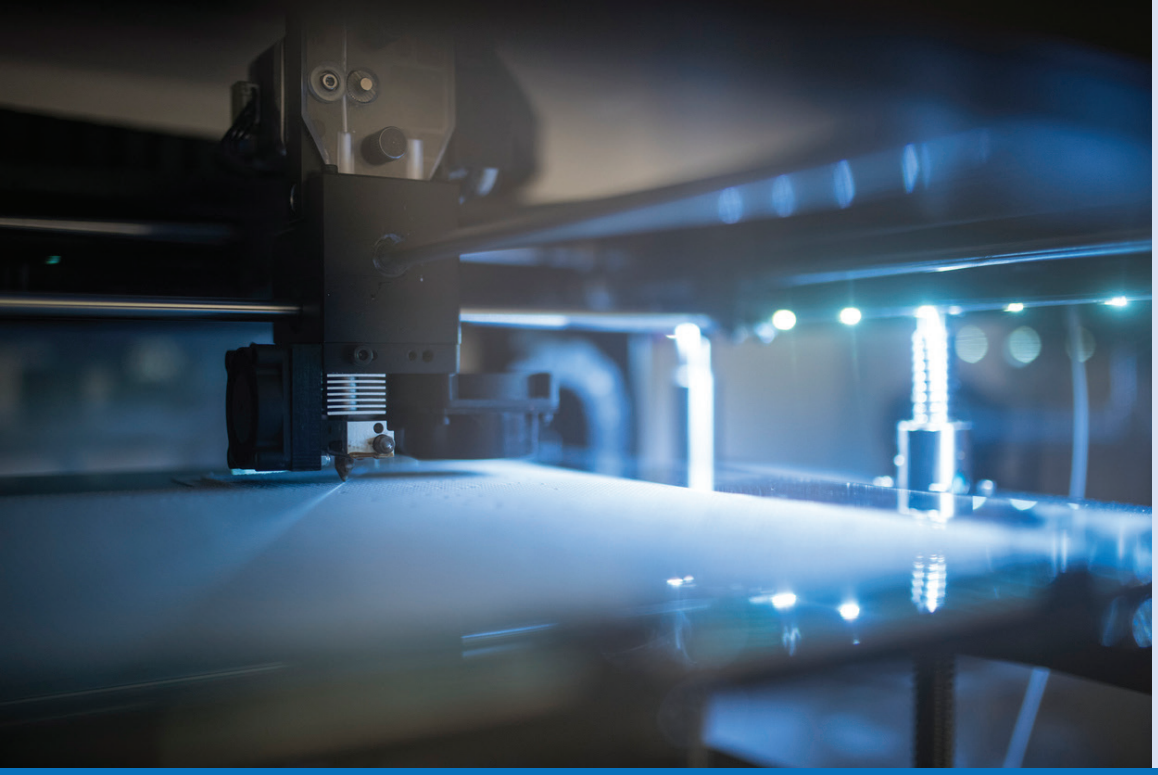

REGULATORY FOCUS

Emerging Technology Integration in FDA's Drug Approval Process

By Monika Jain and Shilpa Rana

This article discusses important aspects of the US Food and Drug Administration's (FDA's) "Emerging Technology Program" with a focus on emerging technology, such as continuous manufacturing and 3D printing, and details what information is to be included in drug submissions. The authors highlight a number of benefits of the program, including the synergy created between FDA and the pharmaceutical industry.

Introduction

An important step in FDA's mission to support pharmaceutical innovation and modernization to protect and promote the public health was the publication of the final guidance, "*Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization*" in September 2017.{1} With this guidance, FDA provided the pharmaceutical industry an opportunity to participate in its "Emerging Technology Program," allowing collaboration between the FDA special group known as the "Emerging Technology Team (ETT)" and pharmaceutical companies interested in using emerging technologies for their regulatory submissions for review by the Center for Drug Evaluation and Research (CDER). Note: products reviewed by the Center for Biologics Evaluation and Research (CBER) are not covered by this program.

The purpose of the emerging technology program is to encourage interested pharmaceutical companies to submit questions and proposals about the use of the specific emerging technology in their drug development program prior to their regulatory submissions to the ETT group, which has a representation from all relevant FDA pharmaceutical quality functions.

FDA Commissioner Scott Gottlieb commented on the program: "In recent years, we've seen significant advances in the modernization of drug manufacturing, including shifts to continuous manufacturing and the first 3D printed drug," he said. "These advancements

have led to improved products for patients and consumers and the opportunity to have a more stable and lower-cost supply chain."{2}

Companies working on the following regulatory submissions can take advantage of the program:

- Investigational New Drug Application (IND)
- Original or supplemental New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA) or Biologic License Application (BLA)
- Application-associated Drug Master File (DMF)

Emerging Technology Program Scope

The scope of the emerging technology program is included in FDA's guidance, "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization." The following are main points:

- Requests to participate in the program will be accepted on the planned submission, which include one or more elements that will be subject to quality assessment, where the agency has limited review or inspection experience.
- The proposed technology has the potential to improve product quality in-line with FDA's mission of improving safety, identity, strength, quality or purity of the drug product.
- This program impacts only the quality sections (Chemistry, Manufacturing and Controls (CMC) and facility related information) of planned submission. The applicant is required to provide justification showing the proposed emerging technology meets previously mentioned criteria or the program's scope.

Emerging Technology Program Participation

Companies interested in FDA's emerging technology program must submit a written request for a "Type C meeting/Pre-ANDA meeting to participate in the emerging technology program" at least three months prior to the planned submission date.{3}

A request of no more than five pages should be submitted to CDER-ETT@fda.hhs.gov.{4} The following details are expected to be included in the written request:

- a brief description of the proposed emerging technology
- a brief explanation of why the proposed emerging technology is substantially novel and unique and should be considered under this program
- a description of how the proposed emerging technology could potentially improve product safety, identity, strength, quality or purity
- a summary of the development plan and any perceived roadblocks to implementation (e.g., technical or regulatory)
- a timeline for a submission of an IND, original or supplemental ANDA, BLA or NDA, or DMF and associated applications

FDA will communicate its decision to the submitting companies within 60 days of the receipt of their request for program participation.

Emerging Technology Program Benefits

This program enables pharmaceutical companies to engage with FDA during early stages of product development (in some cases, even before identification of lead compound) and provides an opportunity for continued interactions on the proposed technology. The opportunity could be used to discuss issues or challenges related to the development of the innovative or novel technology (detailed below) and where FDA has limited review or inspection experience.{5,6}

1. product technology (development of novel dosage form or container closure systems)
2. issues related to manufacturing process (e.g., design, scale-up, and/or lifecycle management)
3. control strategy (testing technology or process controls)

The ETT serves as the primary point of contact to:

- guide participating companies with information required for a planned submission on the emerging technology
- identify and help facilitate regulatory assessment of an emerging technologies with regard to existing legal and regulatory standards, guidance and agency policy related to quality assessment
- lead or co-lead (in partnership with relevant pharmaceutical offices) the review and on-site evaluation and make the final quality recommendation regarding the potential approval of submission in the program
- identify and resolve policy issues to advice on FDA recommendations regarding future submissions that involve the same technology
- Over the last decade, FDA has been developing and implementing similar programs on this topic. Some of FDA's initiative programs include:
- In 2002, *Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach*. {7} This initiative had encouraged early adoption of modern quality assessment systems.
- In 2004, Process Analytical Technology (PAT)—A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.{8} This program promoted the concept of "quality to be built in by design."
- December 2015, *Draft Guidance for Industry on Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base.*{9} This guidance has provided a direction to the industry to modernize pharmaceutical manufacturing.

FDA's continued support to encourage and implement state-of-the-art technologies in product design, pharmaceutical manufacturing and improving quality has helped in the approval of drug products using many modern techniques, such as continuous manufacturing and 3D printing.

Continuous Manufacturing Technology

FDA is taking proactive steps to facilitate the pharmaceutical industry by introducing programs like emerging technology and FDA's manpower resources and guidance. In the last 50 years, there has been significant advancement in technologies used to create drugs. However, there has not been much change in manufacturing processes and most drug makers follow a batch processing method, a step-wise process to manufacture pharmaceutical product.{10} Recent advancements in manufacturing technology have prompted the pharmaceutical industry to consider adopting a continuous manufacturing process, a faster and more efficient way of manufacturing.

Batch manufacturing is a multi-step process in which after each step in the process, production typically stops. For example, to test the sample for quality, sometimes during hold times/between steps, the material may be stored in containers or shipped to another facility to complete the manufacturing. This can add weeks or months to processing time and there is also the possibility of introducing risk to the active ingredient, which is sensitive to the environment.

In contrast, continuous manufacturing is a non-stop drug manufacturing process, within the same facility, without hold time between steps, and eliminates isolated intermediates. In continuous manufacturing, materials are introduced through an assembly line of fully integrated equipment, a process saving time and reducing the possibility of human error. Also, continuous manufacturing has an added advantage of having automated monitoring of the equipment involved, which can detect issues before a failure occurs. In the batch operating system, various operations, such as blending, weighing, compression and coating are conducted in separate rooms at different times, while in continuous manufacturing, all unit operations required to produce a finished drug product are conducted in one room, with one control system.

Food, chemical and petrochemical industries have adopted efficient continuous technology to safely manufacture their products. However, the pharmaceutical industry continues to face the following challenges:

- startup costs for transitioning from traditional manufacturing process to continuous technology
- replacing old equipment with new technology and training staff while maintaining market demand
- uncertainty with regard to how health agencies will react to newly-adopted continuous technology
- There are some key players in the pharmaceutical industry who have taken advantage of FDA's initiative programs and adopted continuous manufacturing process in their drug development and manufacturing stage, including:
- In July 2015, Vertex Pharmaceutical received FDA approval for its cystic fibrosis drug Orkambi® (lumacaftor/Ivacaftor), which is manufactured using the continuous manufacturing process (press release-RAPS.{11}
- For the first time, in April 2016, FDA approved a manufacturing change from batch to continuous for Prezista® (darunavir), a drug for HIV-1 infection.{12} Prezista is manufactured by Janssen Supply Chain (JSC), part of the Janssen Pharmaceutical Companies of Johnson & Johnson (J&J).
- Janssen and J&J are working on their ambitious project of integrating continuous manufacturing in their other range of pharmaceutical therapies with an aim to "manufacture 70 percent of their highest-volume products using continuous manufacturing within next eight years, increasing yield of the drug product by reducing waste by 33 percent, and reducing manufacturing and testing cycle time by 80 percent."{13}

3D Printing and Drug Products

3D printing is an established technology in the medical devices field, dental implants and tailored orthopedics, and is a revolutionary "next step" for the pharmaceutical industry that will enable fabrication of a medicinal product.{14} To date, FDA has cleared more than 85 3D printed devices, most via the 510(k) or emergency use pathways. However, the pharmaceutical industry is still working toward using 3D printing for manufacturing orphan drugs and personalized medicines. Pharmaceutical scientists also are working toward technology advancement to achieve mass production of 3D printed tablets, which will lead expansion of this technology in manufacturing to bulk drug products.

A breakthrough in the use of this technology occurred on 3 August 2015, when FDA approved the first 3D printed drug Spritam (levetiracetam) manufactured by Aprecia Pharmaceutical for the treatment of epilepsy.{15} Spritam® is manufactured using ZipDose® technology combined with 3D printing, which will allow the tablet to disintegrate in the mouth with a little bit of water. 3D printing helps create a porous tablet by forming thin layers of active and inactive ingredients and combining it using aqueous liquid. This structure allows the tablet to dissolve quickly when it comes in contact with water, making it easier to swallow in higher doses as compared to the traditional tablet.

3D printing creates a tablet by building it layer by layer, so it can be tailored/customized per patient. The following are some of the advantages of 3D printing in pharmaceutical manufacturing:{16}

- Assures doctors the customized/personalized tablet they are prescribing will deliver the intended dose.
- Minimizes manufacturing costs for orphan drugs, where typically the market size is considered too small.
- Allows manufacture of tablets in smaller lots as based on market demand instead of the occasional production of one large batch which may limit the available shelf life of the drug product.

Long Term Benefits to the Pharmaceutical Industry

FDA acknowledges that adopting innovative, novel approaches in drug development will present technical and regulatory challenges potentially hindering the progress and use of such technologies. To modernize the pharmaceutical industry, and to identify and resolve potential concerns regarding the use of novel technology prior to regulatory filling, FDA has

proposed the emerging technology program to provide the following benefits to the pharmaceutical industry:{16}

- The pharmaceutical industry will benefit from an early, face-to-face FDA meeting opportunities to discuss the intersection of technical and regulatory challenges at different stages of the drug development program involving novel technologies.
- ETT members will be part of drug development and regulatory submission pathways along with the pharmaceutical company's staff, leading to a more collaborative approach from the beginning of the drug development to its approval stage. **Table 1** identifies potential emerging technology areas in which the pharmaceutical industry can take advantage of FDA's Emerging Technology Program.

Table 1. Potential Emerging Technologies Areas Considered by the Emerging Technology Program{17}

Small Molecules	Biological Molecules	Multiple Products
• Continuous manufacturing of drug substance and drug product • Model-based control strategy for continuous manufacturing • Continuous aseptic spray drying • 3D printing manufacturing • Ultra-long-acting oral formulation	• Controlled ice nucleation for lyophilization processes • Advanced process control such as predictive modelling for process monitoring and close loop bioreactor control • Multi-attribute method • Next generation sequencing • Continuous manufacturing for an upstream process • Pharmacy on demand (a small manufacturing platform for continuous bioprocesses)	• Closed aseptic filling system • Isolator and robotic arm for aseptic filling • Novel container and closure systems for injectable products

Conclusion

FDA's Emerging Technology Program is an example of how pharmaceutical companies interested in using novel technologies can seek guidance, adopt new techniques and open dialogue with FDA at an early stage of product development. Additionally, FDA staff also will get the opportunity to gain knowledge and experience on the use of modern techniques in pharmaceutical manufacturing. The recent approvals of Spritam, manufactured using 3D printing, and Orkambi, manufactured using continuous manufacturing, coupled with the manufacturing change approval obtained by switching to continuous manufacturing process for Prezista (darunavir), are encouraging indications for drug makers hoping to take advantage of FDA's initiative.

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