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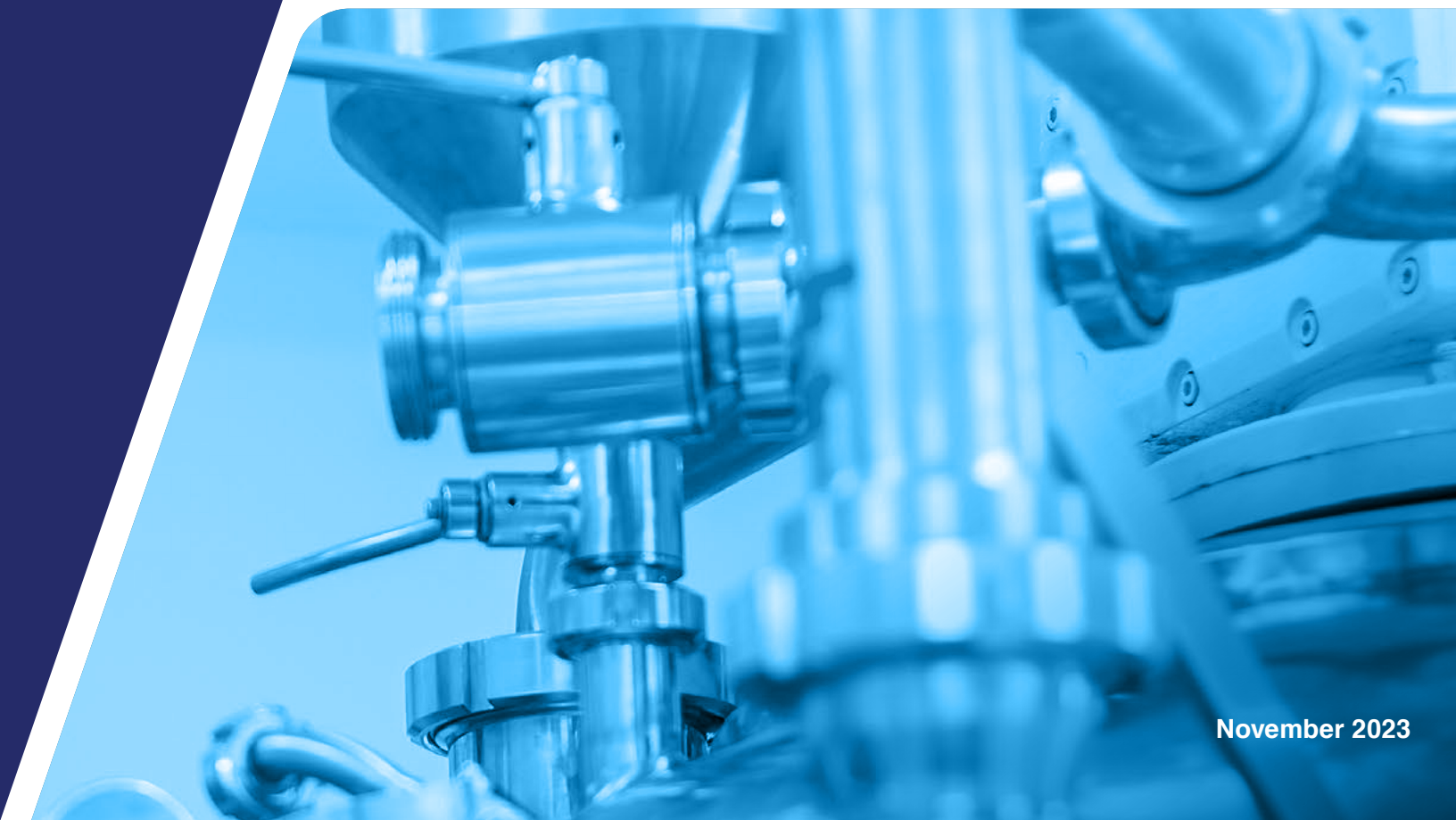
CENTER FOR DRUG EVALUATION AND RESEARCH

# Distributed Manufacturing of Drugs: Stakeholder Feedback and Action Plan



November 2023

*Disclaimer: This paper is for discussion purposes only of stakeholder feedback and is not a draft or final guidance. As such, this document is not intended to convey any current or future requirements, recommendations, or policy related to distributed manufacturing.*

# Executive Summary

FDA's Center for Drug Evaluation and Research (CDER) established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to foster a regulatory framework to support the adoption of advanced manufacturing technologies that could benefit patients. FRAME prioritized distributed manufacturing (DM) and point-of-care manufacturing (POC) as two related technologies that have the potential to advance pharmaceutical manufacturing. The discussion paper *Distributed Manufacturing and Point-of-Care Manufacturing of Drugs* published on October 14, 2022 (October 2022 discussion paper),[1] and the public workshop *The Regulatory Framework for Distributed and Point-of-Care Pharmaceutical Manufacturing: An Opportunity for DM/POC Stakeholder Engagement* was held from November 14 to 16, 2022.[2] To ensure that FDA's evaluation of the regulatory framework for these technologies is thorough, stakeholders were invited to comment on the discussion paper and provide feedback through moderated discussions at the public workshop.

This paper summarizes stakeholder feedback in areas such as terminology, operating models, central and host sites, approaches for meeting product specifications, comparisons to other regulated products, and international harmonization. Stakeholders generally:

- Identified areas in which they seek additional regulatory clarity regarding DM technologies for drugs and biological products[3]
- Seek assurance that regulations and policies are compatible with DM strategies for drugs and biological products
- Seek clarified regulatory expectations to facilitate the implementation of DM for drugs and biological products
- Seek international harmonization on the regulation of DM technologies to facilitate the adoption of DM for drugs and biological products

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[1] For the discussion paper available on CDER's FRAME initiative website at https://www.fda.gov/media/162157/download?attachment, comments were submitted to https://www.regulations.gov, Docket No. FDA-2022-N-2316.

[2] See CDER's FRAME workshop website available at https://www.fda.gov/drugs/news-events-human-drugs/fdapqri-workshop-regulatory-framework-distributed-and-point-care-pharmaceutical-manufacturing.

[3] All references to drugs include both human drugs and biological products (including those regulated by CBER), unless otherwise specified.

In addition to summarizing stakeholder feedback, this paper describes CDER's actions to date and its action plan for the DM regulatory framework in alignment with the four FRAME priorities:

1. Seek and analyze input
    a) Receive input from stakeholders in response to the discussion paper and at the public workshop (*complete*)
    b) Engage participants in the CDER Emerging Technology Program (ETP) and the Center for Biologics and Research (CBER) Advanced Technologies Team Program (CATT)
    c) Incorporate stakeholder feedback to address risks and clarify regulatory expectations (priorities 2 and 3 below)
2. Address risks to ensure that regulations and policy are compatible with future advanced manufacturing technologies
    a) Conduct a comprehensive analysis of regulatory requirements applicable to DM strategies
    b) Assess the ability of FDA's IT systems to receive and store location information and inform inspections
3. Clarify expectations for stakeholders implementing advanced manufacturing
    a) Develop guidance, as appropriate, to clarify areas of regulatory uncertainty (*three proposed draft guidances in development*)[4]
    b) Evaluate existing policy to enable adoption of suitable DM technologies
4. Harmonize regulatory approaches
    a) Publish internationally harmonized guidance for industry *Q13 Continuous Manufacturing of Drug Substances and Drug Products* (March 2023),[5] as many DM units may use continuous manufacturing (*complete*)
    b) Coordinate with international regulatory partners to promote global adoption of DM technologies

[4] See the document titled *CDER Guidance Agenda, New & Revised Draft Guidance Documents Planned for Publication in Calendar Year 2023* (July 2023), available at https://www.fda.gov/media/134778/download.

[5] FDA updates guidances periodically. 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.

# I. Introduction

Advanced manufacturing technologies have the potential to improve the reliability and robustness of manufacturing processes and supply chains and increase timely access to quality medicines. As advanced manufacturing technologies are emerging rapidly, FDA aims to foster a regulatory framework that supports the adoption of advanced manufacturing technologies to benefit patients, keep pace with innovation, and support public health. CDER established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to provide clarity and reduce uncertainty for stakeholders aiming to use advanced manufacturing technologies to produce quality drugs and biological products.[6] FRAME's goal is to identify potential regulatory areas of consideration and develop an action plan to address the regulatory framework for advanced manufacturing technologies. FRAME's four priorities are to:

1. Seek and analyze input to ensure that FDA's understanding of advanced manufacturing technologies for drugs and biological products is thorough and the analysis of the regulatory framework is science- and risk-based
2. Address risks to ensure that regulations and policy are compatible with future advanced manufacturing technologies
3. Clarify expectations for stakeholders implementing advanced manufacturing
4. Harmonize regulatory approaches to ensure that global regulatory practice is clear to stakeholders implementing advanced manufacturing

To address the first priority above, FDA engaged stakeholders on distributed manufacturing (DM) and POC technologies in two different forums. The first was a discussion paper *Distributed Manufacturing and Point-of-Care Manufacturing of Drugs* for public comment in the *Federal Register*.[7] The discussion paper presented areas of consideration and potential policy development identified by evaluating the regulatory framework for DM and POC technologies. The second was a

[6] All references to drugs include both human drugs and biological products (including those regulated by CBER), unless otherwise specified.

[7] See the document titled Discussion Paper: *Distributed Manufacturing and Point-of-Care Manufacturing of Drugs; Request for Information and Comments* that published in the *Federal Register* of October 14, 2022 (87 FR 62416).

3-day public workshop held with the Product Quality Research Institute (PQRI) on *The Regulatory Framework for Distributed and Point-of-Care Pharmaceutical Manufacturing: An Opportunity for DM/POC Stakeholder Engagement* that was held from November 14 to 16, 2022.[8] The public workshop included presentations by stakeholders developing DM and POC technologies and moderated discussion sessions for all participants on areas such as terminology, operating models, central and host sites, the pharmaceutical quality system (PQS),[9] and control strategies and specifications.

The sections of this paper that follow: (1) summarize stakeholder feedback on the DM and POC regulatory framework received through public comments on the October 2022 discussion paper and at the public workshop; and (2) provide a description of FDA's planned actions to address the regulatory framework concerning these advanced manufacturing technologies.

# II. Summary of Stakeholder Feedback

## A. Terminology

The October 2022 discussion paper included terminology describing DM and POC manufacturing, based on preliminary stakeholder engagements[10] regarding these technologies.

In written comments and through discussion during the PQRI workshop, stakeholders provided the following feedback with respect to the terminology used in the October 2022 discussion paper. Stakeholder feedback clarified that not all *DM units* are intended to be mobile (i.e., mobility may not be a defining feature of a DM unit).

Stakeholders noted that the term *point-of-care* (POC) describes a manufacturing location, rather than a manufacturing technology. For example, health care providers might understand the term to mean a location where samples are collected or a test is performed on a patient. Stakeholders shared that POC manufacturing might not always be a subset of DM because, except for some

[8] See the FDA/PQRI workshop agenda and materials available at https://pqri.org/fda_pqri_poc_dm_workshop/.

[9] See the internationally harmonized guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

[10] Preliminary stakeholder engagements include a 2021 report titled *Innovation in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations* issued by the National Academies of Sciences, Engineering, and Medicine, available at https://nap.nationalacademies.org/catalog/26009/innovations-in-pharmaceutical-manufacturing-on-the-horizon-technical-challenges-regulatory, and include industry meetings with ETP and CATT.

applications of so-called *self-contained distributed manufacturing*,[11] POC manufacturing might not be intended to be part of a decentralized manufacturing strategy or entail the use of DM units.

Additionally, stakeholders noted that POC is an existing term used differently in several medical product areas. Feedback highlighted existing products that some stakeholders consider to be made at POC (e.g., certain radiopharmaceuticals covered in 21 CFR part 211 and positron emission tomography (PET) drugs covered in part 212 (21 CFR part 212)). Other products that stakeholders suggested could be considered to be made at POC include human cellular and tissue-based products (HCT/Ps) produced at or near a medical health care facility (HCF) accommodating the patients receiving these products or certain medical devices that process blood or HCT/Ps. Stakeholders shared the concern that any new elements of regulatory framework should avoid disrupting existing POC-related articles, processes, and operations.

## B. DM PQSs

The October 2022 discussion paper presented the following two potential PQS approaches for DM: (1) host sites networked and overseen by a centralized PQS, and (2) a unit with its own PQS (decentralized PQS).

Stakeholders supported the reasoning that a centralized PQS model is essential to DM for CDER-regulated products, especially to ensure regulatory compliance. (See also section II.H below.) Some stakeholders suggested that centralized control over remote manufacturing locations could provide quality oversight by sharing real-time data and documentation through a digital network across a fleet of DM units. Some explained that existing tools, such as cloud-based data management systems and digital connections, could be applied to permit a centralized PQS site to oversee and ensure consistent drug product quality across all manufacturing locations under its control. Stakeholders proposed that a designated person or designated people (e.g., fleet administrators) could be responsible for managing DM units deployed to different host sites. Feedback suggested that information to support that the centralized PQS has adequate oversight of multiple DM units across multiple geographical locations could be provided in a regulatory submission and assessed through facility evaluation.

Stakeholders also suggested that a centralized PQS, similar to traditional manufacturing locations, might help to ensure site-to-site consistency through oversight of starting materials, active pharmaceutical ingredients (APIs), and inactive ingredients for each host site. Some proposed that a centralized inventory

[11] Self-contained distributed manufacturing is not a term that FDA has necessarily adopted, but, for ease of reference, this paper will use this term to refer to the subset of manufacturing that stakeholders consider to be a subset of DM.

might distribute to host sites appropriately sourced, qualified, and released starting materials; APIs; or inactive ingredients. Some feedback also suggested that electronic safeguards, such as kitting and barcoding, could help ensure that only qualified and released raw/starting materials and validated standard operating procedures (SOPs) are used with the manufacturing unit. Some explained that the central site could also collect, hold, and test retention and stability samples to control the consistency of product attributes across manufacturing locations. Stakeholders also stated that deviation, corrective action, and change management through a centralized PQS (rather than a decentralized PQS) might more effectively ensure product consistency across host sites. Some opined that specific mechanisms may be necessary to contemporaneously manage deviations, failure investigations, corrective actions, and changes across a network of host sites. Stakeholders did not address who, either central or local personnel, would need to perform these and other quality system functions.

Stakeholders indicated that a decentralized PQS model may not be preferable for all traditional facilities that manufacture CDER-regulated product due to the need for local control over raw and starting materials and product consistency. In contrast, some stakeholders explained that both centralized and decentralized PQS models may be applicable for some CBER-regulated products. For example, starting materials for these products (e.g., autologous T cells) are patient-specific and may have inherent variability not applicable to CDER-regulated products; thus, different considerations may be needed for their control.

## C. DM Applicants

Stakeholders noted that the types of DM applicants may differ among CBER- and CDER-regulated products. Stakeholders opined that an HCF might be an applicant and responsible for complying with CGMP requirements for CBER-regulated products, such as HCT/Ps; however, some opined that such a model may be less suited for CDER-regulated products. Stakeholders further opined that applicants of CDER-regulated products could either own and operate or contract the site controlling the centralized PQS, similar to contracting a traditional brick-and-mortar contract manufacturing organization.

## D. Operators

Stakeholders posited that traditional manufacturing personnel[12] would likely operate most DM units; however, some predicted that self-contained DM units might be operated by either traditional manufacturing personnel or those affiliated with the HCF hosting the unit. Stakeholders proposed that, in some

[12] See 21 CFR 211.25.

cases, employees of either the applicant or a third-party contractor might operate self-contained DM units. Some suggested that operators might be trained and overseen by the centralized PQS to be responsible for operating a unit at the host site. Multiple stakeholders suggested that the operator of a self-contained DM unit for CDER-regulated products would be responsible for ensuring that the unit is used appropriately (e.g., per approved instructions for use or user manuals) within validated operating conditions and used for completing appropriate training. Others suggested that the operator for CBER-regulated products might be expected to perform extensive operations that include manipulation of raw materials and/or manufacturing equipment and execution of test methods. Some explained that the extent of operational and quality responsibilities delegated to the unit operator might depend on the features of a given technology and the complexity of the product, which in some cases might require an assessment of operator performance at host sites.

Stakeholders stated that a centralized PQS and onboard technology could manage operator access, limiting operation to those who are appropriately qualified. Stakeholders proposed that manufacturers might establish a standardized training strategy to qualify unit operators. Some suggested that such training could be communicated electronically to individual operators at host sites and/or through augmented reality training. In general, stakeholders held the view that standardized training developed and maintained by the centralized PQS can contribute to consistent drug product quality and process performance across all manufacturing locations.

## E. Establishments

The October 2022 discussion paper identified that considering a different approach for registration and listing of DM units may be needed.[13] The discussion paper acknowledged that a DM establishment might consist of mobile DM units connected or networked to a single, centralized PQS.

Although stakeholders explained that manufacturers might maintain real-time location information for mobile units, which could be detected by a global positioning system (GPS), such an approach could potentially raise operational questions. For example, some suggested that CDER's facility catalog may need to accommodate an FDA Establishment Identifier number that is able to identify DM units. Stakeholders proposed various mechanisms for reporting DM unit location changes, such as supplemental applications (e.g., changes being effected supplements), annual reports, and annual updates to master files. Feedback suggested that any such approach would need to be sufficiently timely or frequent,

[13] The regulations in 21 CFR 207.1 define establishment as "a place of business under one management at one general physical location. . . ."

based on the mobility of the technology. Some explained that using existing regulatory processes for frequent updates to an application could be a significant burden on both the applicant and FDA.

Stakeholders stated that current regulations may not need to be modified to accommodate the registration and listing of stationary DM units; however, some explained that manufacturers who operate mobile DM units may be required to make multiple and/or frequent updates to the physical address of the unit identifying each change in location to facilitate inspection by FDA. Stakeholders proposed that manufacturers could register a central site at a fixed location and register a fixed location as part of that registration and identify the mobile DM units under the control of the centralized PQS. Some stakeholders noted that a similar approach is used to register mobile establishments for blood collection.

## F. Changing and Adding Locations of DM Units

The October 2022 discussion paper acknowledged that, under the existing framework, applicants might need to demonstrate bioequivalence and/or generate analytical comparability data, conduct method transfer and validation, and generate stability data for each new location of a DM unit.

Stakeholders stated that the need for these data could be prohibitively burdensome for applicants because DM units may be deployed to different locations within and/or among host sites and may make smaller-than-traditional batch sizes. Although drug product quality should be consistent across all DM units, some stakeholders opined that there may not be a need for comparability, validation, and stability data to support implementation at every new location because the risk to drug product quality may be mitigated if units are demonstrated to be *cloned* or *like-for-like*. However, some stakeholders noted that external factors beyond the DM unit, such as environment, utilities, personnel, and associated control procedures, might need to be controlled to ensure process performance and drug product quality at new manufacturing locations.

Most stakeholders agreed that the performance of DM units at a new location should be evaluated to ensure consistent drug product quality, but many also agreed that the process to submit these data in an amendment or a supplement to an application could burden applicants making multiple or frequent location changes. In addition, they acknowledged that FDA's assessment workload to review such information could drastically increase. As a result, some stakeholders proposed alternative approaches wherein data to support new locations could be generated during product development and submitted and assessed in an original application.

One approach proposed by stakeholders centered on the use of existing assessment tools that have appropriate supporting data, such as comparability protocols and/or identified established conditions, to define criteria that must be met following a move to a new location. Another stakeholder proposal advocated for incorporating DM unit location moves into the process development studies to reduce the data needed to support postapproval moves and/or establish an operational envelope (e.g., qualification/validation and environmental parameters, utility requirements) within which a DM unit would operate. Some explained that there could continue to be a need to perform installation and operational qualification at each new manufacturing location. Stakeholders indicated that the approaches described above for demonstrating product comparability and process consistency could be more challenging for CBER-regulated products, given the types of starting materials (e.g., autologous T cells) and their inherent variability. Generally, stakeholders opined that the scope and nature of the data and information needed to support a new manufacturing location should be informed by the capabilities of the DM unit, the potential risk of a new location to drug product quality, and operator training.

Some stakeholders stated that employing dedicated operators who move with a unit could reduce the risk to process and equipment performance and drug product quality. However, some noted that this type of approach might not be feasible for DM units that move frequently and/or over large geographical distances. In these scenarios, stakeholders noted that new personnel may need to be trained and qualified to operate DM units at each new location.

## G. Inspections

The October 2022 discussion paper acknowledged that FDA's establishment evaluation and inspection functions could face logistical and resource challenges due to: (1) the mobility and dispersion of DM units, (2) an increase in manufacturing locations, (3) the intent to manufacture in or near nontraditional host sites, and (4) the intent to operate beyond one physical location (i.e., centralized PQS and host sites).

The most commonly proposed inspection model by stakeholders was the inspection of a centralized PQS site, conducted on a risk-based frequency consistent with FDA's current procedures for risk-based inspection schedules. Stakeholders also encouraged the use of alternative tools (e.g., remote regulatory assessments) and advanced technology (e.g., augmented reality glasses) for host site assessments.

Another suggested scenario was for FDA to conduct preapproval or prelicense inspections of host sites to support initial DM implementation, and then the

centralized PQS site would perform future host site evaluations that FDA could review when inspecting the centralized PQS site. Stakeholder rationale for this approach was based on the premise that cloned or like-for-like DM units reduce risks to drug product quality. Some explained that other factors, such as host site environmental and microbial controls, that are external to the DM unit at host sites should continue to be subject to FDA evaluation, especially for nontraditional host site environments.

## H. Considerations for Meeting Established Specifications

In general, stakeholders held the view that the intended uses and capabilities of self-contained DM units may impact the ability to use traditional tools to control quality risks. For example, some posited that future host sites may not contain traditional quality control laboratories, and operators may not be traditional manufacturing operators (e.g., quality control analysts). Several stakeholders explained that rapid, nontraditional approaches to release testing might be needed for the viability of self-contained DM units. The most common approach that stakeholders proposed was the use of process analytical technology (PAT) to enable real-time release testing. Although PAT has been developed for manufacturing processes in traditional facilities, stakeholders noted that most of these tools have not been miniaturized to the scale required for a self-contained DM unit. Some stakeholders also proposed approaches that do not rely on real-time or end-product testing, including modeling and digital twins, parametric release, and conditional release. Stakeholders postulated that self-contained DM units could offer an advanced level of understanding about processes and products, which, based on risks, might justify a combination of control approaches. Some stakeholders also supported that appropriate testing strategies may be product or technology specific, and risk assessments might determine whether some uncertainties can only be monitored and controlled through end-product testing.

A particular focus of stakeholders was quality testing for microbial and adventitious agents, which typically generate results within 7 to 14 days and could delay the administration of product to patients. Stakeholders noted that rapid safety testing methods for microbial and adventitious agents have seen limited implementation. Therefore, some stakeholders proposed the potential combination of traditional and emerging methods, with other approaches, to ensure microbial and adventitious agent safety. Some noted that negative-to-date sterility results could permit rapid product release, while traditional testing results could provide confirmation or lead to initiation of risk mitigation measures. Some stakeholders noted that such a process is analogous to the approach used for products with short half-lives (e.g., radiopharmaceuticals) for which sterility testing is performed after a dose has been administered and protocols are established to address a failed sterility

test. Stakeholders also proposed that sterility testing may not be necessary for every batch if a DM unit is a fully closed system that is appropriately validated to consistently manufacture sterile products.

Implementation of DM stability programs was an area of consideration for several stakeholders who noted that the design of stability programs might depend on a given technology and/or product. An example given was drug products intended for patient administration within short time frames. Stakeholders seek guidance on the stability data (e.g., time-points, methods) needed to support short expiry periods.

Batch size was a stakeholder consideration for release and stability testing strategies. Stakeholders noted that self-contained DM units might be designed to produce small batch sizes (even single doses) and noted that destructive end-product testing of such batches may not be feasible. Some stakeholders proposed that samples produced from runs performed immediately before or after a run producing material for patient administration (i.e., sub-batches) might be used for release and stability testing. Some noted similarities between such a proposed approach and the existing approach used for PET drugs. Stakeholders also proposed that samples might be generated by additional process runs (i.e., batches) performed before and/or after the run that produced the dose for patient administration, provided that the samples used for release and stability testing are representative and predictive of the administered batch.

The October 2022 discussion paper also posited that applicants who are not present at host sites will face challenges with ensuring that any rejected manufacturing components are quarantined, disposed of, and investigated.

To mitigate this issue, stakeholders proposed that a centralized PQS could provide oversight and consistency in document management and training, deviation identification and handling, investigations, change controls, corrective actions and preventive actions (CAPA), and batch releases. Stakeholders proposed several approaches to control release of finished products, including using cloud-based and other electronic systems (e.g., artificial intelligence) at the centralized PQS site to review batch records and data and/or make automated decisions about batch disposition (e.g., by using *review by exception* algorithms). Some noted it might be feasible for applicants to perform timely batch review and approval through the centralized PQS for all units at host sites (e.g., time zone-specific teams), while others ventured that sufficiently robust and appropriately validated automated systems might be able to ensure proper batch decisions. Stakeholders did not generally address procedures for handling rejected material at host sites or the processes by which self-contained DM units might physically detain and/or destroy nonconforming products to prevent use. Stakeholders noted that some operators may not be traditional manufacturing personnel and the extent of their quality responsibilities might be limited by their organization, though some noted

that robust process controls might assist in ensuring that only conforming product is administered to patients.

## I. Other Regulated Products and Harmonization

### 1. Other Regulated Products

Some stakeholders highlighted similarities among drug products made in self-contained DM units and PET drugs and other radiopharmaceuticals, noting that such drug products might be made in enclosed, automated systems. Some stakeholders observed that PET drug products typically have short half-lives and, as a result, the final manufacturing step (e.g., radiolabeling) is performed in proximity to patient care. Some noted the unique considerations for ensuring quality of PET drugs in this environment and the specific regulations that cover these products (i.e., part 212). Stakeholders suggested that some approaches used in the regulation of PET drugs could inform the regulation of self-contained DM units due to the potential parallels between the manufacturing of PET drugs and manufacturing in a self-contained DM unit. For example, some noted that processes used to train and qualify manufacturing unit operators and handle and investigate nonconformances at PET sites might inform approaches for self-contained DM units. Additionally, some noted that digital tools (such as cloud-based systems) are currently used to store manufacturing records that a remote site can access and use to ensure drug product quality. Several stakeholders speculated that the testing and release strategies used in the manufacture of PET drugs and other radiopharmaceuticals could be examined for applicability to self-contained DM units.

Some stakeholders cautioned that certain approaches for PET drug manufacturing may not be appropriate for DM. One difference noted was that PET drugs are a narrow pharmaceutical class with distinct qualities that require manufacturing in proximity to patients and for which the HCF is generally the applicant who operates a synthesizer and is responsible for quality oversight and CGMP compliance. Some also noted that certain manufacturing process can be more complex than radiolabeling and might result in higher lot-to-lot variability relative to PET drugs.

Although the October 2022 discussion paper excluded manufacturing units intended for drug compounding (i.e., drugs not adhering to the specification of an approved regulatory submission), stakeholders noted potential parallels between DM and drug compounding. The FRAME initiative continues to focus on products that are the subject of approved applications (i.e., products that would be marketed under a new drug application, an abbreviated new drug application, or a biologics license application).

### 2. International Harmonization

Stakeholders expressed a desire for international harmonization on terminologies and principles to facilitate the adoption of DM. Some suggested that harmonization through global regulatory guidelines (e.g., International Council for Harmonisation, pharmaceutical inspection convention/ pharmaceutical inspection co-operation scheme (PIC/S)) could mitigate uncertainty associated with deployment of manufacturing units to host sites across broad geographical locations. Such an example provided was a central site in one regulatory jurisdiction with host sites in other jurisdictions. Stakeholders were clear that international collaboration among stakeholders and global regulators will be important, as these technologies continue to develop and deploy.

# III. Action Plan Summary

## 1. Seek and analyze input to ensure that FDA's understanding of DM technologies is thorough and analysis of the regulatory framework is science- and risk-based

**Stakeholder Feedback:**

Stakeholders developing DM technologies for drugs and biological products have identified areas in which they seek additional regulatory clarity.

**FDA Action:**

- Publish *Distributed Manufacturing and Point-of-Care Manufacturing of Drugs* discussion paper for public comment to share information with the public and request input on discussion questions related to the regulatory framework.

  **STATUS** Completed with 60-day comment period that closed on December 13, 2022

- In partnership with PQRI, hold public workshop on the *Regulatory Framework for Distributed and Point of Care Pharmaceutical Manufacturing: An Opportunity for DM/POC Stakeholder Engagement* to discuss stakeholder input on these technologies.

  **STATUS** Completed November 16, 2022

- Engage participants in the CDER Emerging Technology Program (ETP) and the Center for Biologics and Research (CBER) Advanced Technologies Team Program (CATT) who are developing DM technologies and visit development sites.

  **STATUS** Ongoing

- Incorporate input and feedback into priorities 2 and 3 below.

  **STATUS** Ongoing

## 2. Address risks to ensure that regulations and policy are compatible with future DM technologies

### Stakeholder Feedback:

Stakeholders seek assurance that regulations and policies are compatible with DM strategies for drugs and biological products.

### FDA Action:

- Conduct a comprehensive analysis of regulatory requirements applicable to DM strategies for drugs and biological products.

  **STATUS** Ongoing

- Assess the ability of FDA's IT systems to receive and store location information and inform inspections.

  **STATUS** Ongoing

## 3. Clarify expectations for stakeholders implementing DM

### Stakeholder Feedback:

Stakeholders seek clarified regulatory expectations to facilitate the implementation of DM for drugs and biological products.

### FDA Action:

- Develop guidance, as appropriate, to clarify areas of regulatory uncertainty, including the following proposed draft guidances: *Considerations for Complying with 21 CFR 211.110, Approaches to Meeting CGMP Requirements for Distributed Manufacturing*, and *Advanced Manufacturing Technologies Designation Program Designated Technologies in Drug and Biological Products*.[14]

  **STATUS** Ongoing

- Evaluate existing policy, incorporating stakeholder feedback, and develop guidance, as needed, to enable adoption of suitable DM technologies.

  **STATUS** Ongoing

[14] See the document titled *CDER Guidance Agenda, New & Revised Draft Guidance Documents Planned for Publication in Calendar Year 2023* (July 2023), available at https://www.fda.gov/media/134778/download.

## 4. Harmonize to ensure that global regulatory practice is clear to stakeholders implementing DM

### Stakeholder Feedback:

Stakeholders seek international harmonization on the regulation of DM technologies to facilitate the adoption of DM for drugs and biological products.

### FDA Action:

- Publish internationally harmonized guidance for industry *Q13 Continuous Manufacturing of Drug Substances and Drug Products.*[15]

  **STATUS** Completed March 1, 2023

- Coordinate with international regulatory partners to promote the global adoption of DM technologies.

  **STATUS** Ongoing

[15] FDA anticipates that many DM units, including self-contained DM units, will use continuous manufacturing.

# Appendix: Abbreviations

Following is a list of abbreviations used in this paper:

| Acronym | Explanation |
|---|---|
| API | Active Pharmaceutical Ingredient |
| CAPA | Corrective Actions and Preventive Actions |
| CATT | CBER Advanced Technologies Team |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CGMP | Current Good Manufacturing Practice |
| DM | Distributed Manufacturing |
| ETP | Emerging Technology Program |
| FRAME | Framework for Regulatory Advanced Manufacturing Evaluation |
| GPS | Global Positioning System |
| HCF | Health Care Facility |
| HCT/Ps | Human Cellular and Tissue-Based Products |
| ICH | International Council for Harmonisation |
| IT | Information Technology |
| PAT | Process Analytical Technology |
| PET | Positron Emission Tomography |
| PIC/S | Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme |
| POC | Point-of-Care Manufacturing |
| PQRI | Product Quality Research Institute |
| PQS | Pharmaceutical Quality System |
| SOP | Standard Operating Procedures |

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