



CENTER FOR DRUG EVALUATION AND RESEARCH

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# Distributed Manufacturing and Point-of-Care Manufacturing of Drugs



*Disclaimer: This paper is for discussion purposes only and is not a draft or final guidance. It is meant to facilitate early input from stakeholders outside the Agency. The Agency intends to consider such input in developing a future regulatory framework. As such, this document is not intended to convey any current requirements or policy related to distributed or point-of-care manufacturing.*

## Introduction

CDER's mission is to ensure that human drugs are safe and effective, meet established quality standards, and are available to patients. To advance this mission, FDA's Pharmaceutical Quality for the 21st Century Initiative promotes an efficient, agile, and flexible pharmaceutical manufacturing sector that reliably produces quality drugs without excessive regulatory oversight. Trends in drug development require more flexibility in manufacturing. The COVID-19 public health emergency highlighted the importance of agility in the pharmaceutical manufacturing sector to enable rapid and localized responses to changing demand.

Advanced manufacturing is a term for an innovative pharmaceutical manufacturing technology or approach that has the potential to improve the reliability and robustness of the manufacturing process and supply chain, and increase timely access to quality medicines for the American public. Advanced manufacturing can: (a) integrate novel technological approaches, (b) use established techniques in an innovative way, or (c) apply production methods in a new domain where there are no defined best practices or experience. Advanced manufacturing can potentially be used for new or currently marketed large or small molecule drugs.

FDA has recognized and embraced the potential of advanced manufacturing. In 2014, CDER established the Emerging Technology Program (ETP) to work collaboratively with companies to support the use of advanced manufacturing. CDER observed a rapid emergence of advanced manufacturing technologies through the ETP and realized that regulatory policies and programs may need to evolve to enable timely technology adoption. The National Academies of Sciences, Engineering, and Medicine issued a 2021 report titled *Innovation in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*, noting potential innovations in integrated, flexible, and distributed manufacturing. These potential innovations include modular approaches to streamlining drug development and production, and the deployment and use of highly portable manufacturing units. Such highly portable units could enable localized point-of-care (POC) manufacturing and precision medicine. Drug manufacturers have recently engaged CDER through the ETP regarding the development of distributed manufacturing (DM) platforms.

## Scope

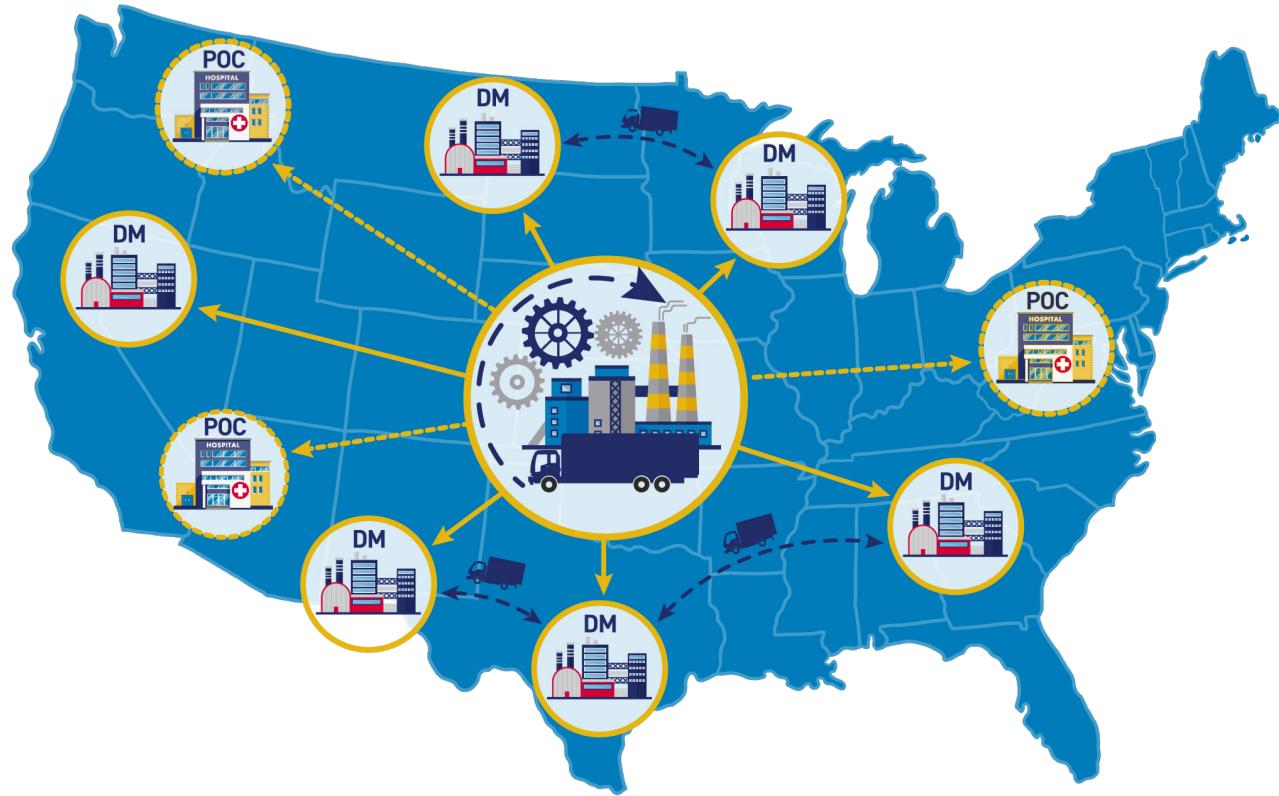
This discussion paper presents areas associated with DM and POC manufacturing that FDA has identified for consideration as FDA evaluates our existing risk-based regulatory framework as it applies to these technologies. CDER scientific and policy experts identified these areas from a comprehensive analysis of existing regulatory requirements applicable to the approval of drugs manufactured using DM and POC technologies. This analysis included a review of applicable statutory provisions, regulations, and guidance related to quality assessment and inspections to determine whether an application presenting an advanced manufacturing technology can fit within our current regulatory framework. The areas of consideration in this discussion paper are those for which FDA would like public feedback.<sup>1</sup> The areas of consideration presented in this discussion paper focus on products that would be marketed under a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA). CDER is releasing this discussion paper to share information with, and gather input from, the public on DM and POC manufacturing. A series of discussion questions after each technology is included to stimulate feedback. This feedback will help inform CDER's evaluation of our existing regulatory framework as it applies to advanced manufacturing technologies to ensure production of quality drugs for U.S. patients. While the initial analysis focused on products regulated by CDER, FDA's Center for Biologics Evaluation and Research (CBER) also expects the development of advanced manufacturing technologies associated with DM and POC manufacturing for products that it regulates. As such, we invite feedback on the discussion questions related to products regulated by CDER and CBER.<sup>2</sup> The scenarios, terminology, and questions that follow are for discussion purposes only and do not connote FDA's approval.

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<sup>1</sup> The areas of consideration and policy development identified in the discussion paper are not exhaustive of all application and CGMP considerations but are critical. The determination of critical areas is based on CDER's analysis of the regulatory framework and stakeholder engagements through the ETP.

<sup>2</sup> All references to drugs include both human drugs and biological products (including those regulated by CBER), unless otherwise specified. CBER is also seeking early input from stakeholders outside the Agency on how the considerations outlined for DM and POC manufacturing may be further tailored to CBER-regulated products considering their uniqueness and for which there may be limited manufacturing experience or undefined critical quality attributes.

# Background



## Terminology

The following definitions are for the purposes of this discussion paper only.

### Manufacturer

A person who owns or operates a facility (site) that manufactures a drug. Manufacturing includes processing, packing, holding, labeling, and testing of a drug product. The term manufacturer includes but is not limited to control laboratories, contract laboratories, contract manufacturers, contract packers, contract labelers, and other entities that manufacture a drug.

### Traditional Manufacturer

Entities which have historically manufactured drugs (e.g., applicants, contract manufacturers) at fixed-location facilities.

## **Applicant**

Any person who submits an NDA, ANDA, or BLA, or an amendment or supplement to an NDA, ANDA, or BLA to obtain FDA approval of a drug or biological product, and any person who holds an approved NDA, ANDA, or BLA.

## **Manufacturing Platform**

A collection of raw materials, software, equipment, and analytics designed to function together to produce drugs at different locations.

## **Manufacturing Unit**

A mobile manufacturing process, including equipment, peripherals, and interfaces, that may be part of a manufacturing platform.

## **Distributed Manufacturing (DM)**

A decentralized manufacturing strategy consisting of a manufacturing platform comprising manufacturing units deployed to multiple locations. Possible use scenarios include:

- Units located within manufacturing facilities operating within the host's pharmaceutical quality system (PQS).
- Units manufactured and installed to the same specifications at multiple manufacturing facilities, networked and operated by a central remote PQS.
- Units as independent manufacturing facilities, each with its own PQS.

## **Point-of-Care Manufacturing (POC)**

A subset of DM that uses manufacturing units distributed to host sites in proximity to patient care (e.g., health care facilities) where:

- Drugs are intended to be administered to patients.
- Manufacturing units are neither intended for personal, in-home use nor drug compounding (i.e., drugs will adhere to the specification of an approved regulatory submission).
- The host sites are not applicants or typical manufacturers and do not source active pharmaceutical ingredients (APIs) or excipients for use in a manufacturing unit.<sup>3</sup>

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<sup>3</sup> For the purposes of this discussion paper, CDER does not envision that health care facilities would be deemed manufacturers. For this reason, end users would not source their own materials.

- The end user is not a traditional manufacturing operator; their quality responsibilities are minimized and in accordance with established instructions by the applicant (e.g., assembling the components of the POC unit and activating validated software).

For the purposes of this discussion paper, the POC-use scenario is a centralized PQS maintained by an applicant who is responsible for:

- Drug produced by the manufacturing platform at all sites,
- Meeting submission/application requirements,
- Complying with CGMP requirements through the production of the finished dosage form, and
- Tracking all manufacturing units.

### **Health Care Facility (HCF)**

A site with responsibility for providing diagnostic, therapeutic, surgical, and other patient services for specific and general medical conditions. HCF personnel may include pharmacists, nurses, physicians, and other clinicians and allied health professionals.

### **End User**

A trained operator of a POC Manufacturing Unit at an HCF. The trained operator may be an employee of the applicant, HCF staff, or a third-party contractor.

# Areas of Consideration Associated with DM

## 1. Mobile manufacturing platforms may not align with traditional manufacturing facility registration and listing

As a general matter, current registration/listing requires manufacturing establishment information such as physical address, phone number, and the name of the owner or operator of the establishment. Mobile units may be moved to multiple physical locations. Current registration regulations generally consider manufacturing units located at different locations to be separate establishments and do not contemplate the mobility of manufacturing units. Therefore, compliance with current regulations may require manufacturers who operate mobile units to make multiple and/or frequent updates of the physical address. Although mobile units may be connected/networked via the internet to a single PQS overseeing the manufacturing platform, they could be considered different establishments under 21 CFR 207.1: “a place of business under one management at one general physical location.” Registration regulations also require the issuance of a unique facility identifier (UFI).

These realities raise operational questions. For example, CDER’s facility catalog (Integrity Application Facilities (IAF)) may need to accommodate an FDA Establishment Identification (FEI) able to track the manufacturing units belonging to a given manufacturing platform. Since the definition of establishment also affects application assessment, the content and format of the facility information in an ANDA, NDA, and BLA may need to accommodate multiple manufacturing units belonging to a manufacturing platform.

### Some Potentially Associated Requirements and Policies

- Sections 510 and 704 of the Federal Food, Drug, and Cosmetic (FD&C) Act
- 21 CFR 207.1, 207.17, 207.25, 207.29, 207.49, and 600.3
- Guidance for Industry:
  - *ICH M4Q: The CTD – Quality* (August 2001)
  - *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers* (October 2019)
  - *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing*
  - *Specification of the UFI System for Drug Establishment Registration* (November 2014)
- Draft Guidance for Industry
  - *Reporting Amount of Listed Drugs and Biological Products Under Section 510(j)(3) of the FD&C Act*<sup>4</sup>

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<sup>4</sup> When final, this guidance will represent FDA’s current thinking on this topic.

## **2. Multiple DM locations may affect FDA's ability to perform manufacturing facility inspections**

In the current regulatory framework, each manufacturing facility is individually evaluated to determine the need to conduct a pre-approval/pre-license and/or surveillance inspection, based on risk. Whether manufacturing units are considered individually or as a cohort for inspection purposes, DM could lead to a significant increase in the number of manufacturing locations associated with a given application. Further, FDA may have to consider the need to evaluate and/or inspect units after they move to new locations. The units' mobility and the increase in manufacturing locations could present logistical and resource challenges to FDA's facility evaluation and inspection functions.

### **Some Potentially Associated Requirements and Policies**

- Sections 505(b), 505(j), 510(h,) and 704 of the FD&C Act; section 351 of the Public Health Service (PHS) Act
- Compliance Programs for Inspections available at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs>

## **3. Each new location of a DM unit may affect the regulatory submission and assessment of manufacturing facility changes**

Applicants may need clarity as to whether or when a manufacturing unit's movement constitutes a manufacturing site change requiring the submission of an amendment or supplement to the application, and the types of information to be provided.

### **Some Potentially Associated Requirements and Policies**

- Section 506A of the FD&C Act; 21 CFR parts 210 and 211; 21 CFR 314.60, 314.70, 314.81, 314.96, 314.97; 21 CFR 601.12
- Guidance for Industry:
  - *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER - Questions and Answers* (October 2019)
  - *ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021)
  - *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021)
  - *Changes to an Approved NDA or ANDA* (April 2004)
  - *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)

- *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
  - *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* (September 1997)
  - *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* (2004)
  - *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994)
- Draft Guidance for Industry
    - *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016)<sup>5</sup>

#### **4. Applicants may need to demonstrate bioequivalence for each new location of a DM unit<sup>6</sup>**

As a general matter, the change in a manufacturing site currently requires an applicant to demonstrate bioequivalence or to provide information sufficient to permit FDA to waive bioequivalence studies. Under a DM paradigm, if each move of a manufacturing unit is considered a site change, an applicant could be required to provide data and information regarding bioequivalence for each move.

#### **Some Potentially Associated Requirements and Policies**

- Section 506A of the FD&C Act; 21 CFR 314.70, 314.97; 21 CFR 320.21
- Guidance for Industry:
  - *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
  - *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* (September 1997)

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<sup>5</sup> When final, this guidance will represent FDA's current thinking on this topic.

<sup>6</sup> "Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 CFR 314.3

- Draft Guidance for Industry:
  - *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs* (March 2014)<sup>7</sup>
  - *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016)<sup>8</sup>

**5. Each new location of a DM unit may cause the applicant to be required to generate analytical comparability, method transfer and validation, and stability data**

If each move of a DM unit is considered a manufacturing facility change, each move could require additional data to support approval of a supplement, including analytical comparability, method transfer and validation, and stability data. The need for these additional data (especially stability data) would burden applicants making multiple and/or frequent location changes and increase FDA's assessment responsibility.

**Some Potentially Associated Requirements and Policies**

- 21 CFR 314.70
- Guidance for Industry:
  - *ANDAs: Stability Testing of Drug Substances and Products* (June 2013)
  - *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014)
  - *ICH Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)
  - *ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005)
  - *Container and Closure System Integrity Testing In lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products* (February 2008)
- Draft Guidance for Industry:
  - *Postapproval Changes to Drug Substances* (September 2018)<sup>9</sup>

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<sup>7</sup> When final, this guidance will represent FDA's current thinking on this topic.

<sup>8</sup> When final, this guidance will represent FDA's current thinking on this topic.

<sup>9</sup> When final, this guidance will represent FDA's current thinking on this topic.

## **6. A central PQS for multiple units and locations may affect the Agency's ability to evaluate the PQS**

In the current application assessment paradigm, each manufacturing facility is evaluated individually considering that facility's PQS and information in an application or application supplement. The internationally harmonized guidance on pharmaceutical quality systems, ICH Q10, recommends that a PQS is primarily assessed at facility level and in alignment with corporate PQS policies. CDER does not have experience evaluating the central PQS of a manufacturing platform of distributed units that move frequently. In such cases, the full quality management system for a DM unit may not be in the physical manufacturing space and may be overseeing multiple locations. Though some quality system activities may be physically conducted at the manufacturing unit, FDA may need to consider how quality management systems should be developed by companies and evaluated by FDA. For example, for a DM unit, a lifecycle assessment approach may be necessary to adequately address risks to product quality over multiple location changes.

### **Some Potentially Associated Requirements and Policies**

- 21 CFR parts 210 and 211
- Guidance for Industry:
  - *ICH Q10 Pharmaceutical Quality System* (April 2009)
- MAPP 5016.1 *Applying ICH Q8(R2), Q9, and Q10 Principles to Chemistry, Manufacturing, and Controls Review* (May 2016)

## **7. The structure of applications may affect the regulatory submission and assessment of multiple drugs to be manufactured using the same DM platform**

The review process for a DM unit may be challenging because of the potential for numerous types of drug products that could be produced by it. FDA's assessment of a drug's manufacturing process and controls considers product-specific risk factors that could affect that drug's quality. For example, a low-dose and a high-dose drug manufactured on the same platform may require different control strategies to ensure the quality of these products. Perceived barriers to producing multiple drugs on a DM unit include the lack of strategies for (1) leveraging prior knowledge to facilitate product development and (2) reducing the filing of redundant information in regulatory applications. FDA may need to consider how to best capture regulatory information on DM units that would be used to produce multiple drugs.

### **Some Potentially Associated Requirements and Policies**

- Section 505 of the FD&C Act; Section 351 of the PHS Act
- 21 CFR parts 314 and 601

## DM Discussion Questions

1. Are there any additional aspects of the current regulatory framework (e.g., aspects not listed above) that may affect DM and should be considered by FDA?
2. Are there new regulations or guidances that would be helpful for providing transparency on DM, and if so, what aspects of DM should be considered?
3. Are there DM use scenarios that are not captured in the discussion paper? Do the areas of consideration still apply? Are there additional areas of consideration?
4. How could the DM unit resemble or differ from that of a manufacturing facility at a fixed location?
5. How should an applicant report the installation or relocation of a DM unit to the Agency?
6. How often would a DM unit be projected to move to a new location?
7. How should an applicant demonstrate comparability of product quality following a DM unit move to a new location?
8. How could a “centralized” quality system (i.e., at the “parent location”) ensure that each DM unit would comply with CGMP requirements and biological product quality standards?
9. Are there additional areas of consideration that should be addressed for DM units capable of manufacturing multiple, different drug products compared to DM units capable of manufacturing a single product?

## Areas of Consideration Associated with POC

POC is a subset of DM and, as such, the points associated with DM identified in the previous section also apply to POC. Additional areas of consideration described in this section relate to DM units in proximity to patient care (e.g., at HCFs).

### **1. POC units operated by end users in new host site environments may affect the applicant’s ability to comply with CGMP and registration regulations**

Currently traditional manufacturers are responsible for manufacturing processes and controls. However, scenarios in which end users, who are not traditional manufacturing operators or under the control of such manufacturers — operating POC units at the point of care are being contemplated. Sites hosting POC units (e.g., HCFs) to produce a drug would not be typical regulated drug manufacturing entities and may not have all the capabilities of a typical manufacturing site. It may be a challenge for applicants to ensure the quality of supplies and materials, maintain robust automated systems for manufacturing unit controls, develop instructions to operate units as validated, conduct root cause analyses in the event of quality system failure, and host record systems such that all

required records are created and maintained for review. For example, the development of manufacturing unit controls may be challenged by the need to minimize interventions by the end user and to account for variations in the POC unit host site environment (e.g., moving the unit within the host site, temperature/humidity of the host site) that may affect the quality of the finished product.

#### Some Potentially Associated Requirements and Policies

- 21 CFR 207.1, 207.25, 207.49, 207.57, 207.69, 600.3, 807.3, and 807.21
- 21 CFR 211.25, 211.28, 211.134, 211 Subpart J, 600.10

## 2. POC units operated by end users in new host site environments may affect the applicant's ability to use traditional tools to meet drug quality standards

The current regulatory framework includes requirements intended to ensure product quality, such as the testing of input components (e.g., raw materials) prior to manufacture and testing of the finished drug product. Challenges may arise if a POC unit or host site does not contain a traditional quality control laboratory (i.e., one that conducts off-line testing for product release), produce sufficient doses for traditional destructive quality control sampling and testing (i.e., those that consume the sample), or keep reserve samples as part of cGMP obligations. In-process materials and input components may require sampling and testing through alternative mechanisms (e.g., integrated or automated analysis) or through alternative control strategies (e.g., process model controls). Applicants will face challenges to ensure that any rejected manufacturing component will be quarantined and disposed of or investigated. This may require archiving and evaluation of production and final drug product conformance records based on sophisticated computerized approaches (e.g., cloud-based data storage).

Applicants who are not present at the host site may face challenges in maintaining proper control over product labeling, including how drugs made in the POC platform will be appropriately packaged and labeled prior to dispensing to a patient. The final drug product from a POC unit may be intended for administration within a short timeframe after production. FDA may need to consider the data needed to support the product expiry date and overall product quality, especially in cases where traditional microbial tests or annual stability programs may not be feasible or pragmatic.

#### Some Potentially Associated Requirements and Policies

- 21 CFR 211.22, 211.84, 211.86, 211.89, 211.100, 211.101, 211.110, 211.130, 211.134, 211.137  
211.142, 211.160, 211.165, 211.166, 211.167, 211.170, 211.192, 211.194, 610.10, 600.12, 610.2
- Guidance for Industry:
  - *ICH Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)
  - *ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996)

- *ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000)
- *ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)
- *ICH Q8(R2) Pharmaceutical Development* (November 2009)
- *ICH Q9 Quality Risk Management* (June 2006)
- *ICH Q10 Pharmaceutical Quality System* (April 2009)
- *ICH Q11 Development and Manufacture of Drug Substances* (November 2012)
- *Process Validation: General Principles and Practices* (January 2011)

### **3. POC units operated by end users in new host site environments may affect the Agency's ability to conduct inspections**

Currently, an applicant's PQS resides at the traditional manufacturing facility; however, a POC applicant's PQS may reside at the location responsible for the PQS of the platform, while product may be generated at non-traditional host sites (e.g., HCFs) by POC units. This dynamic would affect FDA's ability to evaluate facilities. For example, a pre-approval inspection of the PQS facility may include the review of POC unit controls and data generated at host sites; however, the examination of product and the observation of interactions between the end user and the POC unit at the host site may be challenging depending on the number of POC units and how they are deployed. FDA may be challenged by the need to assess quality at all or multiple POC unit host sites during an inspection at the location where the PQS resides.

#### **Some Potentially Associated Requirements and Policies**

- 21 CFR 211, 600.21, 601.20(a)(1), 601.20(a)(2), and 601.20(d)
- Guidance for Industry:
  - *ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry* (September 2016)
  - *ICH Q9 Quality Risk Management* (June 2006)
  - *ICH Q10 Pharmaceutical Quality System* (April 2009)
- Compliance Programs for Inspections available at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs>

**4. POC platforms capable of producing diverse doses and strengths may affect the applicant's ability to conform to the approved drug specifications**

POC platforms may be capable of producing drugs with a range of doses, rather than fixed strengths, and with different excipient mixtures. Unique drugs can be produced on a single POC platform (e.g., different concentrations of a single drug substance or different combinations of multiple active ingredients); however, drug manufacturers must receive approval for each drug product made under the application, and finished dosage forms must meet the specifications approved in the applications. Applicants may face challenges developing safeguards to ensure that only the approved drug product(s) meeting specification can be made on the POC unit. Based on previous interactions, applicants might have questions on the distinction between POC drug manufacturing and drug compounding. Applicants may also have trouble developing adequate cleaning procedures or other design controls to prevent cross-contamination between different products produced on the same unit.

**Some Potentially Associated Requirements and Policies**

- 21 CFR 314.50, 601.2, and 211.67

## **POC Discussion Questions**

1. *Are there additional aspects of the current regulatory framework (e.g., aspects not listed above) that may affect POC and should be considered by FDA?*
2. *Are there new regulations or guidances that would be helpful for providing transparency on POC, and if so, what aspects of POC should be considered?*
3. *What type of business relationships are envisioned between companies developing POC platforms and health care facilities (HCFs)? For example:*
  - a. *POC platform manufacturer co-located at HCF and operates platform locally*
  - b. *POC platform manufacturer operates platform remotely with qualified HCF staff as end users*
  - c. *HCF purchases and operates POC manufacturing platform*
4. *What mechanisms are needed for the maintenance and validation of the POC unit at the host site?*
5. *What are the necessary steps and elements for the qualification and training of end users? What safeguards should be in place to ensure that only the qualified, trained end user operates the POC platform?*
6. *What steps are necessary to ensure the quality of materials (APIs, excipients, processing aids, container-closure systems) distributed or sold to POC end users and that only qualified components are used in the POC platform?*

7. What mechanisms are needed to ensure deviations will be identified and prevented, and nonconforming drug is rejected or segregated?
8. A POC unit may be operated in a designated location at the host site (e.g., hospital pharmacy) or be moved to different locations (e.g., a patient's bedside). What additional potential locations are envisioned for the POC unit operation, if any?
9. How might records of the drug manufactured in the POC platform and dispensed by the end user be created, maintained, and made available?
10. Do the areas of consideration apply to POC for biological products where end users would be expected to perform extensive preparation or substantial manipulation (e.g., cell isolation, cell processing, combining with scaffolds, etc.) of the product at the HCF? Are there additional unique areas of consideration for these products?
11. Are there aspects of POC platforms that have not been considered in the discussion above?

## Conclusion

This discussion paper presents areas for additional consideration and potential policy development that CDER identified based on evaluating the application of the existing regulatory framework to DM and POC activities. A regulatory framework for advanced manufacturing evaluation will address these areas while also considering how potential changes could affect existing technologies and facilities. CDER will use feedback submitted to the docket to inform future policy development. Please submit your comments regarding this discussion paper to <https://www.regulations.gov>, Docket No. FDA-2022-N-2316.

# Appendix A

## References—Potentially Associated DM and POC-related Guidance, Regulations, Compliance Programs, and Other Documents

### Distributed Manufacturing (DM)

#### FDA Guidance for Industry

[ANDAs: Stability Testing of Drug Substances and Products](#) (June 2013)

[ANDAs: Stability Testing of Drug Substances and Products Questions and Answers](#) (May 2014)

[Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products](#) (July 1997)

[Changes to an Approved NDA or ANDA](#) (April 2004)

[Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products](#) (June 2021)

[ICH M4Q: The CTD — Quality](#) (August 2001)

[ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management](#) (May 2021)

[ICH Q12: Implementation Considerations for FDA-Regulated Products](#) (May 2021)

[ICH Q1A\(R2\) Stability Testing of New Drug Substances and Products](#) (November 2003)

[Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers](#) (October 2019)

[Process Validation: General Principles and Practices](#) (January 2011)

[Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing](#) (May 2009)

[Specification of the Unique Facility Identifier \(UFI\) System for Drug Establishment Registration](#) (November 2014)

[Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice](#) (September 2004)

[Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products](#) (November 1994)

[SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation](#) (November 1995)

[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](#) (October 1997)

[SUPAC-SS: Nonsterile Semisolid Dosage Forms, Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation](#) (May 1997)

## FDA Draft Guidance for Industry

[Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations](#) (March 2014)<sup>10</sup>

[Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information](#) (April 2016)<sup>11</sup>

[Postapproval Changes to Drug Substances](#) (September 2018)<sup>12</sup>

[Reporting Amount of Listed Drugs and Biological Products Under Section 510\(j\)\(3\) of the FD&C Act](#) (October 2021)<sup>13</sup>

## CDER Manual of Policy and Procedures

[MAPP 5016.1 Applying ICH Q8\(R2\), Q9, and Q10 Principles to Chemistry, Manufacturing, and Controls Review](#)

## Compliance Program

7346.832 [Pre-Approval Inspections/Investigations](#)

7356.000 [Inspections of CDER-led or CDRH-led Combination Products](#)

7356.002 [Drug Manufacturing Inspections](#)

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<sup>10</sup> When final, this guidance will represent FDA's current thinking on this topic.

<sup>11</sup> Ibid.

<sup>12</sup> Ibid.

<sup>13</sup> Ibid.

7356.002A [Sterile Drug Process Inspections](#)

7356.002F [Active Pharmaceutical Ingredients](#)

7356.002M [Inspections of Licensed Biological Therapeutic Drug Products](#)

## **Code of Federal Regulations, Title 21**

§ [207.1](#): What definitions and interpretations of terms apply to this part?

§ [207.25](#): What information is required for registration?

§ [207.57](#): What information must registrants submit when updating listing information and when?

§ [207.69](#): What are the requirements for an official contact and a United States agent?

§ [207.49](#): What listing information must a registrant submit for a drug it manufactures?

§ [210](#): Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

§ [211](#): Current Good Manufacturing Practice for Finished Pharmaceuticals

§ [314](#): Applications for FDA Approval to Market a New Drug

§ [320.21](#): Requirements for submission of bioavailability and bioequivalence data.

§ [601](#): Licensing

§ [607.3](#): Definitions

## **Point-of-Care (POC)**

### **FDA Guidance for Industry**

[ICH Q10 Pharmaceutical Quality System](#) (April 2009)

[ICH Q11 Development and Manufacture of Drug Substances](#) (November 2012)

[ICH Q1A\(R2\) Stability Testing of New Drug Substances and Products](#) (November 2003)

[ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products](#) (July 1996)

[ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances](#) (December 2000)

[ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products](#) (August 1999)

[ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry](#) (September 2016)

[ICH Q8\(R2\) Pharmaceutical Development](#) (November 2009)

[ICH Q9 Quality Risk Management](#) (June 2006)

[Field Alert Report Submission: Questions and Answers](#) (July 2021)

[Process Validation: General Principles and Practices](#) (January 2011)

## **Compliance Program**

7346.832 [Pre-Approval Inspections/Investigations](#)

7356.002 [Drug Manufacturing Inspections](#)

## **Code of Federal Regulations, Title 21**

§ [211](#): Current Good Manufacturing Practice for Finished Pharmaceuticals

§ [314](#): Applications for FDA Approval to Market a New Drug

§ [600.10](#): Personnel

§ [600.21](#): Time of inspection

§ [601](#): Licensing

§ [610.1](#): Tests prior to release required for each lot

§ [610.12](#): Sterility

§ [610.14](#): Identity

§ [610.2](#): Requests for samples and protocols; official release

# Appendix B

## Acronyms

Acronym	Explanation
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BE/BA	Bioequivalence/Bioavailability
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CMC	Chemistry, Manufacturing, and Controls
DM	Distributed Manufacturing
ETP	Emerging Technology Program
HCF	Health Care Facility
FEI	FDA Establishment Identifier
IAF	Integrity Application Facilities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MAPP	Manual of Policies and Procedures
NDA	New Drug Application
OPQ	Office of Pharmaceutical Quality
POC	Point-of-Care Manufacturing
PQS	Pharmaceutical Quality System
SUPAC	Scale-Up and Post-Approval Changes
UFI	Unique Facility Identifier



**U.S. FOOD & DRUG  
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**Office of Pharmaceutical Quality**

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

10903 New Hampshire Avenue

Silver Spring, Maryland 20993