Discussion Paper: **FDA-2022-N-2316 Distributed Manufacturing and Point of Care Manufacturing of Drugs**

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT (optional)
Digitization can be a very strong enabler of DM and POC Manufacture and can assure data integrity and equivalence of each manufacturing unit. Please consider: • consistency that digitisation of the manufacturing process would bring towards ensuring DM / POC modules are operating in a standardized manner, underneath a centralized PQS. • further, the electronic management of PQS processes, including QC test results review and release can ensure inclusion and visibility across DM / POC modules of real-time tracking and trending data.
It is important to consider how DM or PoC can reduce risk. For example: • use of semi or fully-automated and digitised advanced manufacturing technology using single-use components. • the reduction in dependency on sterile manufacturing personnel in the case of automated or semi-automated technology facilitating a lesser-graded background • standardization of technology and digital twinning of each DM / POC unit under a common PQS consideration (e.g., multiple equivalent DM / POC modules co-designed and operated under one PQS)
There are several questions that we are hoping can find some degree of resolution. For example, the question around what qualification activities are necessary at each site could be addressed following a risk-based approach towards validation, that takes into account identical elements across sites such as processes and PQS. This could be applied to equipment and process qualification, in-process holds, microbial monitoring, resin lifetime, etc.

Specific Comments on the Text ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Comments
Terminology Section (pg 5)	Definitions of DM and POC	Please clarify the difference (if any) between DM and POC. Strictly POC means having the technology literally right beside the patient's bedside, where DM is proximal manufacture. The intent behind the Point of Care definition is recognized (i.e., there are additional categorical concerns when the end-user is not a traditional manufacturing operator), however, it can be confusing, and misaligned with the current use of the term Point of Care, to exclude traditional manufacturers who may manufacture in a unit at/close to a Health Care Facility from the Point of Care definition.
DM Area of Consideration #4	Applicants may need to demonstrate bioequivalence for each new location of a DM unit	One approach may be to focus on the module design and integrated technology being equivalent rather than have to show that the product is equivalent as the manufacturing processes and conditions are identical under one PQS. SUPAC guidelines could be extended to include Manufacturing Module as a unit from which to measure equivalency. Another approach is to conduct risk assessments to demonstrate a level of risk and to determine what needs to be done to demonstrate equivalence based on risk level. E.g. equivalent equipment, raw material suppliers, digital systems, etc. may reduce risk significantly, enabling regulatory flexibility towards requirements (for equivalence and other considerations listed in DM Areas of Consideration #5).
DM Question 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?	The considerations for Distributed Manufacturing should include the potential for mobile units to relocate across multiple health authority jurisdictions. International alignment is needed for the implementation of this technology. ISPE recommends that FDA engage other health authorities that are active in this area, such as MHRA, and eventually advance the topic for alignment through international organizations such as ICH, PIC/S, or ICMRA
DM Question 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?	Please consider additional clarity regarding each of the points of consideration. This would be helpful to align approaches across industry, as well as FDA reviewers and inspectors. Lack of clarity on regulatory acceptability will inhibit the utilization of the technology • In particular, the SUPAC guidance should be updated to accommodate scenarios where the risk of a site "change" (e.g. relocation or replication to add a new unit) is

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		less than a traditional site change, and lesser documentation requirements, or lesser SUPAC "level" may be acceptable. • Where regulations/guidelines listed in the discussion paper are not updated, clarification on how existing guidelines can be flexibly interpreted to support the new technology should be provided. A global approach (such as via ICH guidelines) would be helpful
DM Question 3	A) Are there DM use scenarios that are not captured in the discussion paper? B) Do the areas of consideration still apply? C) Are there additional areas of consideration?	A) Within the definition of DM, please consider adding a "hoteling" scenario where one company's modular unit is housed within another organization's facility. B) Yes, the areas of consideration listed in the paper are still applicable. C) Additionally, consider composing the document to be fully inclusive of small molecule drugs, biotechnology products, and biological products. In several places, the document refers to "drugs" which seems to exclude biotechnology and biological products.
DM Question 4	How could the DM unit resemble or differ from that of a manufacturing facility at a fixed location?	There are many aspects of the DM unit that can "belong" to the unit that typically would "belong" to a traditional manufacturing facility, but that could be shared across DM units at different locations. These aspects include the equipment, the data collection systems, the environmental controls, the batch documentation, the product and unit procedures, and any required end-product QC testing. Aspects that "belong" to the host facility likely include raw material receipt and dispensing, warehousing, personnel, utilities, and perhaps also QC testing (ideally the DM unit would include PAT and RTRT).
DM Question 5	How should an applicant report the installation or relocation of a DM unit to the Agency?	In instances where the unit may relocate frequently (e.g., multiple times a year) or there is a large "fleet" of related DM units at different locations, it would be beneficial for there to be a technology solution to enable real-time awareness (web portal / dedicated email address). The degree of regulatory notification (e.g., Annual Report, CBE, or PAS) should depend upon the product(s) and process within the unit; a risk assessment, examining aspects that might be different at a different location and their impact, could be provided as part of a comparability protocol for upfront agreement on reporting category. For units that maintain a high degree of similarity across locations (e.g., same process and equipment, same composition, same environmental controls, same master batch records) a risk assessment, in addition to product knowledge (e.g., what API/DP/process characteristics

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		may impact CQA, platform experience) could justify a lower reporting category, such as an AR in some instances.
DM Question 6	How often would a DM unit be projected to move to a new location?	The frequency of a DM installation or move is highly variable, depending upon the product and process it supports. This could span multiple moves a year for a transportable, field-based unit (e.g., an emergency response or clinical formulation), or installation of a new replicated unit several years after the initial unit is installed. Tracker technology is available that can provide time and location stamps (an audit trail of the move) and this could eventually eliminate the need to make specific submissions (with appropriate controls and process/product knowledge maintained under the PQS). The tracker can provide alerts to exceptions only.
DM Question 7	How should an applicant demonstrate comparability of product quality following a DM unit move to a new location?	A risk assessment can identify the elements needed to demonstrate comparability. There is an opportunity for flexibility in expectations compared to a traditional manufacturing site move, based upon a reduction in risk compared to a traditional manufacturing site change. For example, in vitro bridging rather than in vivo bioequivalence studies, reduced number of process qualification batches and extent of process validation, and concurrent stability may be warranted. The comparability of product quality following a DM relocation should be risk-based. The expectations could be captured upfront through an approved PACMP/comparability protocol. There is also the possibility that the platform approach data can be leveraged across products and sites to reduce the number of registration lots, share stability data, etc.
DM Question 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?	A centralized PQS can set forth the standards and expectations that are applied regardless of location and drives the expectations for any local procedures in place (if the DM unit is housed in a host facility, for example). Where necessary, enterprise and cloud-based systems, such as change or deviation management systems, may also be accessed at a global level. Enterprise systems can include the history of each DM unit; this is an advantage and can enable trending/tracking - over time, and across all units. The requirements for CGMP oversight between a centralized quality system and a remote DM unit are fundamentally no different than the current approach of a manufacturer's

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		oversight of multiple manufacturing facilities, CMOs, and suppliers. Advances in digital technologies aid in real-time oversight of remote units.
DM Question 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?	The same approach could be applied to DM units that manufacture different DP within the same unit; a comprehensive risk assessment that considers all products and processes should be completed to identify the risks to product quality that arise due to differences in location. Cleaning and segregation, and disposable parts, are all approaches used currently in brick-and-mortar facilities. Digital tools that can "tag" materials and disallow entry into the wrong room could also be implemented. Training will also be critical. There is also the possibility that the platform approach data can be leveraged across products to reduce the number of registration lots, share stability, etc.
POC Question 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?	Please consider clarification in regulations related to compounding vs. pharmaceutical manufacturing for customized dosage forms. In particular, the difference between the two (once ongoing litigation has demonstrated a clear answer). Additionally, 21 CFR 300.50, related to the fixed-dose combination may need to be revisited to allow for patient-specific, convenience dosage forms manufactured under POC.
POC Question 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?	Kindly consider current regulations and guidelines that inhibit the utilization of POC. Consider additional clarification on how existing guidelines can be flexibly interpreted to support the new technology. A lack of clarity on regulatory acceptability may inhibit the utilization of the technology. For example: • It is unclear to some what is expected regarding training for HCF, e.g., who maintains training records. How much of the company's PQS and practices need to be provided to the HCF, and how much is the HCF responsible for. If POC platforms involve the use of 3D printing at the hospital labs (e.g., as in the case of 3D printers based on patient-specific anatomy), a regulatory framework around the quality systems, validation requirements, and data management would be helpful. For example, considerations for user SOPs, training, control of print files, handling the disposition of bad prints, storage and transportation, and material handling.

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POC Question 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	All of these examples are under consideration; note that scenario A could be an Innovator company or a CDMO as a platform manufacturer.
POC Question 4	What mechanisms are needed for the maintenance and validation of the POC unit at the host site?	Standardized and integrated platforms can be developed to validate and maintain POC units, which could be similar to current approaches for PET (positron emission tomography) drugs. The use of digital tools can ensure consistency. There are questions regarding who performs tactical oversight, e.g., who is responding to alarms and provides maintenance, but there are several answers (traveling maintenance, qualified vendor visits, etc.), and these should be incorporated into operations and policies
POC Question 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?	The level of burden differs if operators are from the platform manufacturer, or if operators are the host company/HCF end-users (current CGMP expectations are sufficient for the platform manufacturer). If HCF is the end-user, there could be technology solutions to ensure individuals are adequately qualified and trained before accessing/logging in (e.g., log-in controls, or even biometric log-in).
POC Question 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?	Current GMP expectations are sufficient to assure the quality of materials distributed to and used by POC end users. Flexibility may be needed to satisfy expectations for sampling and storage of raw materials (e.g., test and retain at supplier ship rather than at each end-user site and qualify transportation for materials that may be impacted).
POC Question 7	What mechanisms are needed to ensure deviations will be identified and	We can apply digital solutions to minimize complexity and time dependency challenges (already in use for autologous processing) where the high volume of batch records for

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	prevented, and the nonconforming drug is rejected or segregated?	individualized treatments can be challenging. Incorporation of PAT can aid in ensuring the nonconforming drug is rejected, and movement towards enclosed, automated systems will help in preventing deviations.
POC Question 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?	Other locations may include "in the field" operations for military or emergency response (e.g., regenerative therapies – printing tissue, and wound care). There could also be used in clinical studies (e.g., mobile units that manufacture and administers).
POC Question 9	How might records of the drug manufactured in the POC platform and dispensed by the end user be created, maintained, and made available?	Current GMP expectations are sufficient to manage records for drugs manufactured in the POC platform and dispensed to the end user; the approaches could be similar to those currently used for PET (positron emission tomography) drugs. Additionally, digital solutions such as cloud-based platforms are available to store templates and completed records, and this can be accessed from any location. These systems are already in place for many companies.
POC Question 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?	Yes, the considerations for POC for biological products could be utilized for complex biological products. Any limitations to the technology should be based on physical considerations of the processing areas and equipment and not regulatory barriers related to a fixed physical location of the manufacturing. One could approach the HCF similarly to the approach for raw material suppliers, e.g., qualify them to ensure they meet expectations for training, procedures in place, etc. Additional unique considerations: If in an autonomous environment (in the field) additional controls around the supply chain would be required (e.g., may not be able to pre-qualify).
POC Question 11	Are there aspects of POC platforms that have not been considered in the discussion above?	Please consider modification of the POC definition on pages 5-6 adding inclusiveness of drug substance processing to allow for the broadest potential applicability of this technology to personalized medicines using biotechnology or biological manufacturing.