



December 13, 2022

Dockets Management Staff (HFA-305)
Docket No. FDA-2022-N-2316
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-N-2316, “Discussion Paper: Distributed Manufacturing and Point-of-Care Manufacturing of Drugs; Request for Information and Comments”

Dear Dockets Manager:

The Association for the Advancement of Blood and Biotherapies (AABB) is pleased to submit comments to the Food and Drug Administration (FDA) in response to the recently released discussion paper entitled, “Distributed Manufacturing and Point-of-Care Manufacturing of Drugs.” AABB commends FDA for its work to evaluate the existing regulatory framework as it applies to advanced manufacturing technologies, including distributed manufacturing (DM) and point-of-care (POC) manufacturing.

Background

AABB is an international, not-for-profit association representing institutions and individuals involved in transfusion medicine and biotherapies. The Association is committed to “making transfusion medicine and biotherapies safe, available and effective worldwide.” AABB works toward this vision by developing and delivering standards, accreditation, and educational programs that focus on optimizing patient and donor care and safety. AABB individual membership includes physicians, nurses, scientists, researchers, administrators, medical technologists, and other health care providers.

AABB’s accreditation program started in 1958, and for more than 20 years, AABB has been applying its core principles of quality and donor and patient safety to the field of cellular therapy through its prestigious *Standards for Cellular Therapy Services* (CT Standards) and its related Accreditation program. The CT Standards cover all elements of procuring, manufacturing, and administering cellular therapy products, including the procurement, storage, transport, testing, processing, packing, labeling, distribution, administration, and patient outcomes for these products. AABB’s CT Standards are the foundation for AABB’s accreditation program for cellular therapies.

Additionally, since 1995, AABB has had deemed status to conduct inspections under the Clinical Laboratory Improvement Act (CLIA) for the Centers for Medicare & Medicaid Services (CMS). CMS recognizes AABB for cellular therapy services, transfusion medicine, blood donor activity, immunohematology reference laboratories and molecular testing laboratories. AABB’s accreditation program is also recognized by the U.S. Department of Health and Human Services,

Health Resources and Services Administration (HRSA) and the National Marrow Donor Program/Be The Match (NMDP/BTM). Additionally, AABB is the only accreditor in the United States, and one of only 24 accreditation programs worldwide, that is accredited by the International Society for Quality in Health Care External Evaluation Association (IEEA), the leading global health care external evaluation program.

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?

AABB encourages FDA to consider its historical experience with ensuring the safety, quality, and consistency of biologics developed through DM models when evaluating policies to inform advanced manufacturing models. Additionally, AABB recommends that FDA consider a regulatory framework for advanced manufacturing models that includes extant regulations and guidances as well as third party standard-setting and accreditation organizations.

For example, blood products and biotherapies, including novel cell and gene therapies such as chimeric antigen receptor (CAR) T-cell therapies, are often manufactured through DM models that are governed by FDA regulations and guidances. Further, blood products and human cells, tissues, and cellular and tissue-based products (HCT/P) (21 CFR 1271) are typically administered under a DM model. The FDA's regulations and guidances are supplemented by standards and accreditation programs, including AABB's standards and accreditation programs. While we understand that the purpose of the Discussion Paper was directed towards products subject to Section 351 of the Public Health Service Act, AABB encourages FDA to consider existing blood and HCT/P distributive manufacturing models. By harmonizing future and extant frameworks, the FDA can synergize approaches requiring the continued safety of minimally-manipulated products while facilitating future availability of HCT/Ps as starting materials for advanced therapies. Collectively, the FDA regulations, guidances, and the standards and accreditation programs promote quality, comparability, and process controls.

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?

AABB urges FDA to promulgate regulations or guidances for DM that recognize relevant standards and accreditation programs, including AABB's *Standards for Cellular Therapy Services* (CT Standards) and its related accreditation program. Biotherapies, such as cell and gene therapies and regenerative medicine therapies, already utilize a DM model, and AABB's accreditation program, which is based on the CT Standards, ensures the safety, quality, and consistency of the products.

The CT Standards define the policies, processes, and procedures integral to the maintenance of a quality management system essential to collections of cellular starting material (CSM), which include organizational requirements, equipment qualification, process control, change management, recordkeeping, management of nonconformances, and specifics regarding the establishment of agreements with sponsors and other ancillary facilities to designate appropriate

authority and ensure accountability. AABB accredited facilities are experts in FDA-compliant cell donor qualification, collection, handling, and testing, and many facilities have been performing leukapheresis collection procedures for decades using established policies, procedures, and quality controls. AABB's CT Standards support these longstanding policies, processes and quality management systems by leveraging evidence-informed practices and process improvements to mitigate variability in the collection of cellular starting materials (CSM) for biotherapies, as well as further manufacturing and administering these products to human subjects.

Biotherapies are inherently variable and complex. Thus, requirements and standards are most helpful when they focus on processes, methods, and quality systems that support an integrated risk-based approach, rather than relying on prescriptive specifications or a la carte procedures that may have a deleterious effect if introduced without consideration of the broader systems-level outcomes. For example, equipment varies from location to location in DM. Requirements for quality programs that ensure appropriate validation and qualification for the intended purpose is an essential feature to achieve the desired outcomes across multiple facilities. Standards support these objectives and are independently verified through accreditation programs.

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?

AABB encourages FDA to consider the DM and POC manufacturing models widely utilized for biologics, including blood and biotherapies, when evaluating its risk-based regulatory framework as it applies to advanced manufacturing technologies. It is important to recognize that there is heterogeneity in the definitions provided in the discussion paper. For example, a host site may be a health care facility (HCF) or may be a clinic, blood collection establishment or laboratory, such as a cellular therapy laboratory. Additionally, DM models likely will include varying degrees of remote medical, quality, operational, or administrative oversight. Thus, activity-based definitions may be helpful to recognize the importance of a quality continuum without categorically describing facility types.

4. How could the DM unit resemble or differ from that of a manufacturing facility at a fixed location?

There may be a variety of ways that a DM unit differs from a fixed location, which depend on the function of the DM unit. For example, biohazardous waste management, supply storage, and environmental monitoring may operate differently on a mobile unit as compared to a fixed location. Further, mobile device connectivity with computer systems for conveyance of critical data and manufacturing lot release is a factor that warrants validation and verification. In addition, training and competency of staff may differ depending on the activities being performed. However, each of these functions must be considered uniquely and collectively as part of an overarching quality program to ensure that the complexities of any given scenario are recognized and adequately addressed.

Blood establishments have historically utilized mobile DM units for blood collection, a GMP-regulated activity (21CFR 606 and 21 CFR 640). HCT/Ps may be procured in a hospital surgical

suite or a clinic procedure room subject to FDA regulatory oversight (21 CFR 1271 Subpart D). These are examples of DM that exist today under FDA regulations. AABB encourages the consideration of these regulatory approaches to DM.

5. How should an applicant report the installation or relocation of a DM unit to the Agency?

AABB encourages FDA to consider how it regulates blood collection establishments and certain HCT/P facilities when considering what information it wants related to DM units. Blood collection establishments and certain HCT/P facilities are required to register with the FDA (21 CFR 607 and 21 CFR1271 Subpart B) and submit Annual Reports. There is not a requirement to report specific details about locations of mobile activities of a DM unit.

6. How often would a DM unit be projected to move to a new location?

In the setting of HCT/P and blood collection establishments, DM units move daily, sometimes to multiple locations. Blood collection establishments are required to register their fixed site locations. Mobile collections are considered to be “under” the fixed site registration and the medical director responsibility.

Looking towards the future, it is conceivable that mobile cell collection for cell and gene therapies could expand patient access and reduce the geographical barriers experienced today. AABB encourages FDA to consider existing models for HCT/Ps and blood collection establishments when examining the level of reporting necessary for DM.

7. How should an applicant demonstrate comparability of product quality following a DM unit move to a new location?

AABB encourages FDA to demonstrate comparability of product quality through evidence of accreditation that demonstrates the establishment and maintenance of quality management systems. FDA may consider additional criteria for applicants to demonstrate the comparability of product quality from a DM unit, such as following the applicable FDA regulations and manufacturers’ guidelines as well as establishing reliability through well-characterized and defined collection or manufacturing parameters.

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?

The quality system should be comprehensive, fit for purpose, and inclusive of DM. AABB Standards dedicate a specific section to the importance of agreements between DM facilities, even if they are housed within the same “parent location.” The AABB CT Standards require agreements to be defined, implemented, and periodically reviewed for DM from point of origin to the point of final disposition. AABB accreditation evaluates parent facilities and ancillary sites, including mobile units, assuring chain of identity, chain of custody, and continuity of the

quality system. This ensures an integrated overarching quality systems approach that that is activity-based.

Under AABB's model, if ancillary sites only collect the product, the sites are listed under the parent and AABB assesses them under the umbrella of the parent site accreditation on a scheduled basis. If the ancillary sites engage in manufacturing by doing more than collecting the product (i.e., they engage in activities such as labeling, processing, testing, etc.), the sites would be considered subsidiary sites and would need to be assessed individually and separately accredited.

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?

AABB recommends that FDA recognize standards and accreditation programs that provide a quality and safety framework for facility-defined procedures. AABB encourages FDA to mitigate variability in cellular starting material, which can be used to manufacture single products or multiple, different drug products, by promoting comparability and process controls through mechanisms such as recognizing relevant standards and accreditation programs, such as AABB, and establishing a third-party assessor program. Leveraging existing process controls and compliance mechanisms, such as AABB's standards and accreditation programs, will promote voluntary standardization, safety and quality while reducing unnecessary regulatory burdens.

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?

Please see the response to question 1 under DM Discussion Questions above.

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?

Please see the response to question 2 under DM Discussion Questions above.

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.

As recognized by FDA, AABB understands that there are a variety of different business models related to POC manufacturing. AABB Standards require that agreements are inclusive of roles, responsibilities and quality characteristics.

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?

These factors are typically defined in agreements between the sponsor/manufacturer and the POC providers.

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?

Third party standards and accreditation programs can help ensure the quality of materials distributed or sold to POC end users and that only qualified components are used in the POC platform. For example, the AABB CT Standards require agreements between facilities to be defined, implemented, and periodically reviewed for DM from point of origin to the point of final disposition.

7. What mechanisms are needed to ensure deviations will be identified and prevented, and nonconforming drug is rejected or segregated?

Third party standards and accreditation programs, including AABB's CT Standards, contain relevant requirements and can help ensure that deviations will be identified and prevented, and that nonconforming biologics will be rejected or quarantined.

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?

There are therapies in development that may be administered outside of the hospital setting of care. For example, a POC unit may be located in a blood center, surgical suite, or in another community-based settings.

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?

The manufacturing of products regulated under section 351 of the Public Health Service Act (PHSA) begins at the time when the cells become more-than-minimally-manipulated. In generally, this begins after the collection, handling and infectious disease testing of cellular starting materials (CSM). Until the cells or tissues become more than minimally manipulated, these cells, cell-based products, or tissues are subject to Good Tissue Practices (GTPs) (21 CFR 1271 Subpart D). Section 361 products are subject to the definitions in 21 CFR 1271 Subpart A). AABB encourages FDA to retain this well-established regulation.

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If you have any questions or need additional information, please contact Linda Barnes, DrPH, MHA, RAC, Vice President, Biotherapies at lbarnes@aabb.org.

Sincerely,

[signatures on file]

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