Blood Centers of America's comments to the CDER Discussion Paper "Distributed Manufacturing and Point-Of-Care Manufacturing of Drugs"

Blood Centers of America (BCA) is appreciative that FDA is considering and discussing current and future Distributed Manufacturing (DM) and Point-of-Care (POC) manufacturing needs with industry. Independent community blood centers throughout the United States have a long history of effective and safe collection, processing, and storage of biological material in their independent outpatient facilities from which they supply on-demand to hospitals for therapeutic use. As technologies and regulations have developed, the processing of these blood-based biological materials have been increasingly done at blood centers in closed, highly-automated systems managed, by highly trained and qualified personnel, within the context of increasingly complex facility-based quality control systems and highly regulated cGMP environments.

These blood centers and our colleagues at the Centers for Biologics Evaluation and Research (CBER), as well as other centers and offices at the FDA, have a long history of working together to ensure that the infrastructure, methods, and regulatory oversight assures the safety of the US blood supply. More recently we have leveraged this partnership to support the development and commercialization of cellular therapies incorporating blood-based biological materials. While there are many different methods and technologies employed in providing DM and POC manufacturing, our comments below are directed specifically to cellular and regenerative Medicine therapies.

Blood centers have played a pivotal role in the development of cellular therapies by collecting peripheral blood mononuclear cells (PBMCs) used for 'stem cell' transplantation as well as starting materials and/or manufacturing components for autologous and allogeneic cell therapies including CAR-T products. Additionally, many blood centers have installed and validated cGMP-compliant manufacturing suites with semi-automated manufacturing equipment such as the CliniMACS Prodigy® Platform and the Quantum® Cell Expansion System. These capabilities, implemented through well-established 21 CFR 211 cGMP and 21 CFR 1271 cGTP compliant quality management systems, position blood centers to provide regionalized, POC manufacturing.

Our centers are well positioned to provided cGMP compliant POC manufacturing leveraging the structure set forth in 21 CFR 1271, subpart B, for registration of tissue establishments. This regionalized POC manufacturing approach eliminates the need to move cell therapy equipment from one hospital to another and ensures equipment and facilities are validated for their intended use prior to distribution of therapeutic agents. Additionally, this approach allows FDA to leverage its current regional field services offices to inspect regulated activities occurring within their geographical areas of responsibility.

BCA has compiled the following comments for consideration.

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3	Scope	BCA agrees with the analysis that advanced manufacturing technologies are being actively and rapidly developed which will soon have the potential to offer DM and POC manufacturing of CBER-regulated products.
5	Terminology - "Distributed Manufacturing (DM)	BCA believes DM units will, for the foreseeable future, more likely fall within the first 2 possible use scenarios.
5	Terminology – "Point-of-Care Manufacturing (POC)"	BCA is unclear that POC manufacturing is necessarily a subset of DM but could also be used as a subset of 'centralized manufacturing' where point-of-care or near-point-of-care processing is required by an Applicant and is performed in a POC unit.
6	Terminology – "Point-of-Care Manufacturing (POC)"	BCA believes it is possible, though not the only possible use scenario, that the DM-use scenario also employ a centralized PQS which is maintained by and for which the Applicant is responsible for the requirements currently listed under the POC-use scenario.
7-11	Areas of Consideration Associated with DM – sections 1-7	BCA believes that the implementation and oversight of DM and POC units (along with associated inspection, training, movements, validations, etc.) and the biological inputs and outputs from such systems could be easier to manage within the existing, highly regulated, distributed, and near point-of-care facilities of national blood centers than it could be within patient care facilities or a network of newly established facilities built for the purpose.

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		With its current infrastructure of independent but centrally connected blood centers, blood centers have deep familiarity, experience and expertise with: • regulatory oversight and compliance, • the requirement of a biological supply relationships with local patient care facilities, and • closed and highly-automated units which process biological material within a lower-class clean room environment than is currently required for advanced therapy manufacturing under s.351 regulatory requirements. US based blood centers engaged in interstate commerce are already licensed blood establishments, and many are also registered tissue establishments. This registration process, with its existing mechanisms and infrastructure at FDA, could be leveraged for and extended to DM and/or POC manufacturing. Licensed blood establishments have been providing POC manufacturing for decades by collecting, testing, and manufacturing products used for transfusion and transplantation, as well as collecting autologous based cell therapies. When necessary, blood centers have a long history of transporting equipment from a registered blood/tissue establishment to another location to perform a specific manufacturing step. These remote manufacturing processes occur by the registered facility and are evaluated during routine FDA inspections. The FDA already routinely inspects licensed blood establishment and registered tissue facilities and has dedicated and trained resources for this purpose. With dedicated quality management staff and mature quality systems, licensed blood establishment and registered tissue facilities have a long history of cGMP and cGTP compliance. Such centers would be the most natural locations for DM and/or POC manufacturing given their history with the FDA and regulatory compliance regarding quality systems, record keeping, personnel training, etc.

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		Licensed blood establishment and registered tissue facilities are well versed in installation, validation and maintenance of complex equipment used to manufacture biologic products including having established procedures for validation, including installation qualification (IQ), operating qualification (OQ), and product/process qualification (PQ). Licensed blood establishment and registered tissue facilities have established environmental monitoring system and programs designed to ensure that there is no contamination and cross contamination. Licensed blood establishment and registered tissue facilities can perform many of the Traditional Manufacturer functions and comply with the corresponding obligations given that they already operate as Manufactures or Traditional Manufacturers or supplier of biological material to them or Applicants. Licensed blood establishment and registered tissue facilities have existing transportation systems and validated shipping methods that allow delivery for POC use. Licensed blood establishment and registered tissue facilities currently utilize BECS systems that track biologicals from vein to vein; donor to patient. .
12	DM Discussion Question 1	BCA believes it possible that the current regulatory framework of holding the Applicant responsible for the compliance of a drug product produced by a Manufacturer to be transferrable and applicable to a Manufacturing Unit. Just as now the Applicant is held responsible for drug product produced by the Manufacturer but also the Manufacturer's sites are inspected and must submit validation data, we believe the Applicant could still be held responsible for the drug product produced by the Manufacturing Unit. In this case the manufacturer of the Manufacturing Unit could produce sufficient master validation data such that each host of a manufacturing unit would then be held responsible for verifying compliance and comparability. The host site would be responsible for personnel training and qualification and the PQS but the Applicant would be ultimately responsible for ensuring that the host site has compliant training and PQS to ensure the compliance of their drug product. Independent blood centers are capable of complying with such a paradigm in ways that patient health care facilities are not.

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12	DM Discussion Question 2	BCA believes some type of Masterfile equivalent for DM and POC Manufacturing Unit validation data would be useful.
12	DM Discussion Question 3	As suggested above, we believe the need for POC manufacturing (or at least minimal manipulation-type processing) may be evolving even for drug products that are produced in a centralized manufacturing model.
12	DM Discussion Question 4	BCA believes the DM Manufacturing Units may involve more interconnectivity either to each other or to/through a centralized data collection, process monitoring, and/or control module than is currently the case for fixed location facilities though increasingly the equipment in such facilities has the ability to be connected to cloud-based data systems outside the fixed facility in which it is hosted or are enabled to store data which can be electronically or physically transferred outside the fixed location.
12	DM Discussion Question 5	This could easily be addressed in a similar fashion to the HCT/P establishment listing requirements.
12	DM Discussion Question 6	We do not anticipate such DM units will be frequently relocated.
12	DM Discussion Question 7	As suggested above, we believe a model of comparability verification against a master file of validation data is feasible and likely should be expected upon relocation of a DM unit.

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12	DM Discussion Question 8	BCA believes a "centralized" quality system would be highly beneficial to ensuring compliance of each DM unit, its operation, and the drug product being output from such units. Leveraging networks which have distributed sites around the country, such as BCA, and which already have some level of connectivity, collaboration, and centralization would make the oversight of such DM units much easier than in the initial phase of implementation than using non-networked facilities or providers.
12	DM Discussion Question 9	BCA believes it is more likely that DM Manufacturing Units will be capable of manufacturing multiple, different drug products (versus single products) and consequently the FDA would be better served to focus regulation based on this assumption. Nonetheless we anticipate it would be expected and reasonable for such units to be uniquely listed and licensed per each drug product it is used to produce. Furthermore, in the model described above, each unit would be verified against the master validation data for each drug product it is intended to be used to produce.
12-15	Areas of Consideration Associated with DM – sections 1-7	BCA believes that the implementation and oversight of DM and POC units (along with associated inspection, training, movements, validations, etc.) and the biological inputs and outputs from such systems could be easier to manage within the existing, highly regulated, distributed, and near point-of-care facilities of national blood centers than it could be within patient care facilities or a network of newly established facilities built for the purpose. With its current infrastructure of independent but centrally connected blood centers, blood centers have deep familiarity, experience and expertise with: • regulatory oversight and compliance, • the requirement of a biological supply relationships with local patient care facilities, and • closed and highly-automated units which process biological material within a lower-class clean room environment than is currently required for advanced therapy manufacturing under s.351 regulatory requirements.

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		US based blood centers engaged in interstate commerce are already licensed blood establishments, and many are also registered tissue establishments. This registration process, with its existing mechanisms and infrastructure at FDA, could be leveraged for and extended to DM and/or POC manufacturing. Licensed blood establishments have been providing POC manufacturing for decades by collecting, testing, and manufacturing products used for transfusion and transplantation, as well as collecting autologous based cell therapies. When necessary, blood centers have a long history of transporting equipment from a registered blood/tissue establish to another location to perform a specific manufacturing step. These remote manufacturing processes occur by the registered facility and are evaluated during routine FDA inspections. The FDA already routinely inspects licensed blood establishment and registered tissue facilities and has dedicated and trained resources for this purpose. With dedicated quality management staff and mature quality systems, licensed blood establishment and registered tissue facilities have a long history of cGMP and cGTP compliance. Such centers would be the most natural locations for DM and/or POC manufacturing given their history with the FDA and regulatory compliance regarding quality systems, record keeping, personnel training, etc. Licensed blood establishment and registered tissue facilities are well versed in installation, validation and maintenance of complex equipment used to manufacture biologic products including having established procedures for validation, including installation qualification (IQ), operating qualification (OQ), and product/process qualification (PQ). Licensed blood establishment and registered tissue facilities have established environmental monitoring system and programs designed to ensure that there is no contamination and cross contamination. Licensed blood establishment and registered tissue facilities can perform many of the Traditional Manufacturer functions and comply with the corresponding obligations given that they already operate as Manufactures or Traditional Manufacturers or supplier of biological material to them or Applicants.

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		Licensed blood establishment and registered tissue facilities have existing transportation systems and validated shipping methods that allow delivery for POC use. Licensed blood establishment and registered tissue facilities currently utilize BECS systems that track biologicals vein to vein; donor to patient.
15	POC Discussions Question 1	BCA believes that independent blood centers are sufficiently near the point-of-care with a long-history of providing on-demand, real-time biological material to patient care facilities for use in therapeutic treatment and patient care, that they can be considered a reasonable surrogate for POC Manufacturing units. Because of these centers are more accustomed to the regulatory obligations of such biological material processing than HCFs, they should be considered a more logical location for POC Manufacturing Units.
15	POC Discussion Question 2	BCA believes some type of Masterfile equivalent for DM and POC Manufacturing Unit validation data would be useful.
15	POC Discussion Question 3	BCA believes a logical business relationship between the POC platforms and HCFs is one in which the local blood center purchases and operates the POC manufacturing platform per the specification of and its obligation to its client, the Applicant. The host of the POC manufacturing platform – in this case, the blood center – would be responsible for ensuring both platform and drug product compliance through applicable testing as required by the Applicant. In turn the blood center stores the drug product output by the POC manufacturing platform until such time as it is provided to the HCF on demand.
15	POC Discussion Question 4	We do not envision this has to be much different than the maintenance and validation of equipment currently used for collecting, processing, and validating biological materials but appropriately scaled based on a risk-based analysis. As discussed above, individual unit and host verification of compliance against a master file of multicenter validation data would be a useful paradigm here.

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15	POC Discussion Question 5	We do not envision this has to be much different than the end user qualification and training currently in place for Manufacturers of advanced therapies. The ultimate responsibility would be on the Applicant which, in turn, would rely on the host of the POC manufacturing system. Again, putting such systems into facilities which are already accustomed to the requirements of equipment/manufacturing personnel qualification and training would make such oversight easier especially in the first phases of implementation. Independent blood centers are examples of such facilities. Additionally, such centers, and the organizations which represent them (e.g., BCA, AABB, ISCT, FACT), are actively involved in the education, training, and certification of such personnel,
15	POC Discussion Question 6	We do not envision this has to be much different than the end user qualification and training currently in place for Manufacturers of advanced therapies. The ultimate responsibility would be on the Applicant which, in turn, would rely on the host of the POC manufacturing system. Again, putting such systems into facilities which are already accustomed to the requirements of materials controls, raw material testing, quarantines, etc. would make such oversight easier especially in the first phases of implementation. Independent blood centers are examples of such facilities and certainly more accustomed to such requirements and the systems and controls needed to ensure compliance to such regulations than are HCFs.
16	POC Discussion Question 7	Such POC manufacturing systems will have to incorporate, integrate with, or facilitate sufficient testing capabilities as are required to ensure product failures or contaminations are identified and nonconforming drugs are rejected or segregated. Again we do not see that the ultimate responsibility for this would have to necessarily shift from the Applicant (where it lies today) who would then rely on the POC manufacturing system manufacturer and the host to ensure compliance.
16	POC Discussion Question 8	As discussed above, BCA believes that independent blood centers are sufficiently near the point-of-care with a long-history of providing on-demand, real-time biological material to patient care facilities for use in therapeutic treatment and patient care, that they can be considered a reasonable surrogate for HCFs and ideal hosts for such POC units. Because these centers are more accustomed to the regulatory obligations of such biological material processing than HCFs, they should be considered a more logical location for POC Manufacturing Units.

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16	POC Discussion Question 9	We don't believe the batch records for drug manufactured in POC units has to necessarily differ from those expected to be produced by Traditional Manufacturers. Clearly the connectivity of such units to cloud-based systems may be envisioned as enabling more centralized and easier oversight of such records.
16	POC Discussion Question 10	BCA believes a risk-based analysis is the most appropriate way to regulate POC manufacturing systems based on the level of manipulation such a system, and the drug product for which it is being used, requires. We believe the most likely near-term uses will be for minimal manipulation such as post-thaw 'activation' (involving little-to-no expansion, no differentiation or other manipulation), isolation, and/or washing or other forms of reagent or excipient removal.
16	POC Discussion Question 10	BCA has no additional considerations to add at this time.

As previously stated, BCA appreciates that FDA has invited industry to provide feedback concerning the current and future state of POC cell therapies. We would welcome the opportunity to continue dialogue as the agency builds the regulatory framework required to ensure that the public is provided with therapies that are safe, pure and potent.

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