WHITEPAPER

Regulatory Considerations for Decentralized Manufacturing of Personalized Cell Therapies: A Path Forward for Commercialization of Decentralized Manufacturing of CAR-T Cell Therapies

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CAR-T cell therapies offer potentially curative treatment options for cancer patients who run out of available standard care such as chemotherapies and monoclonal antibody based targeted immunotherapies. Unprecedented efficacy data for leukemias and lymphomas have led to FDA approval several autologous CAR-T cell therapy for these B-cell malignancies including Kymriah®, Yescarta®, Tecartus®, and recently Breyanzi® with many on the horizon. In addition, two more autologous CAR-T cell therapies, ABECMA® of Celgene Corporation (Bristol-Myers Squibb) and CARVYKTI™ of Janssen Biotech, Inc. for relapsed or refractory multiple myeloma have been approved as well.

One of the most important aspects for successful commercialization of CAR-T cell therapy is product manufacturing, quality controls and lot release testing. In the accompanying White Papers in this series, the differences and pros/cons of centralized and decentralized manufacturing paradigms were compared (see also Zhu, 2018).

Although the traditional centralized manufacturing paradigm offers tight controls over the manufacturing process, quality control and lot release testing, it does require in most cases cryopreservation during storage and transportation of both apheresis products as the starting material and the final therapeutic cell products between the central manufacturing sites and the hospitals for collecting patient cells and infusion of the final cell product. In addition, the logistical burden to ship and storage and ensure chain-of-identity (COI)/chain-of-custody (COC) integrity is high, time consuming and costly.

In contrast to the centralized manufacturing paradigm, in this series of White Papers (Centralized vs. Decentralized Manufacture of Personalized Cell Therapies) we have proposed and described a decentralized manufacturing paradigm we termed as "place-of-care manufacturing" in which the CAR-T cell product is made within the hospital or clinic's own facilities. In this setting, automation plays a key role with a closed-system such as the Prodigy System (Miltenyi Biotec) in place to prevent adventitious agent contaminations and cross-contaminations between product runs. A place-of-care manufacturing system is likely to have a much lower cell storage and shipping cost, due to the manageable number of patients being treated in any one hospital at any given time. This lower logistical cost is expected to significantly reduce the cost while maintaining product quality.

One critical question to ask is how the FDA will regulate the decentralized "place-of-care manufacturing system" from a CGMP (Current Good Manufacturing Practices) compliance point of view (21 CFR Parts 210, 211 & 21 CFR part 600-680)? The FDA has already allowed place-of-care manufacturing system for early-stage clinical trials[1,2,3] indicating the manufacturing controls in

[1] Zhu F, Shah N, Xu H, Schneider D, et. al., Closed-system manufacturing of CD19 and dual-targeted CD20/19 chimeric antigen receptor T cells using the CliniMACS Prodigy device at an academic medical center. Cytotherapy. 2018 Mar;20(3):394-406.

[2] Dropulic, B et al. Automated and Decentralized Manufacturing using Lentiviral vectors. ASGCT 22nd Annual Meeting 2019.

[3] Shah, N. N., Johnson, B. D., Schneider, D., Zhu, F.,et. al. (2020). Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nature medicine, 26(10), 1569–1575. https://doi.org/10.1038/s41591-020-1081-3

place are adequate for phase I/II clinical studies. However, a clear regulatory pathway to a Biologics License Application (BLA) approval is much less certain as the full statutory requirements of CGMP compliance may present regulatory challenges. Here we discuss the potential challenges and possible strategies to meet the regulatory expectations for place-of-care manufacturing paradigm during the BLA approval process.

The FDA regulates certain so-called human cells, tissues, and cellular and tissue-based products (HCT/P) under 21 CFR Part 1271. HCT/Ps are defined in 21 CFR 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient in a hospital setting. Examples include, but are not limited to, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissues. An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets certain criteria (21 CFR 1271.10(a) and 21 CFR 1271.15) and does not need to meet the FD&C Act, and/or section 351 of the PHS Act (42 U.S.C. 262) which regulate drug, device, and/or biological product.

The FDA considers gene modified cellular products such as CAR-T cell therapies as a biological product regulated under Section 351 of the PHS Act and/or the FD&C Act. From a Chemistry Manufacturing and Controls (CMC) standpoint, a CAR-T cell product must comply with 21 CFR Part 600-680 as well as 21 CFR Part 210 and 211 (CGMP). The concept of decentralized place-of-care facilities for manufacturing CAR-T cell product under CGMP compliant conditions in a hospital setting is new to the FDA. This will undoubtedly require a new regulatory framework and perhaps novel regulatory policies based on risk assessment on the part of the FDA.

One of the key CGMP requirements is manufacturing process validation (process validation) (21 CFR 211.100(a) and 211.110(a)) that provides a high degree of assurance that the product meets all the attributes it is intended to possess. The challenge is how to perform process validation in decentralized place-of-care manufacturing facilities in multiple hospital sites to support a BLA. One potential approach to meet the process validation requirement in a decentralized place-of-care manufacturing setting depends on several considerations. Key to manufacturing process control is the automated and closed cell manufacturing unit (such as CliniMACS Prodigy) which has several key parameters to control each step of the process including cell seeding, washing, activation, vector transduction, cell expansion, harvest, and formulation. It should be possible to design a prospective process validation protocol to show the automated closed manufacturing units can yield a safe, pure and potent cell product that meets the predefined specification on a consistent basis. However, variability is the biggest enemy of manufacturing process validation. The process should be designed to minimize any source of variability. Perhaps the biggest source of variability is the starting autologous patient cells. Control of the manufacturing process despite starting material variability should be the top priority throughout the product development lifecycle.

Lot release testing in a place-of-care setting warrants careful consideration. The goal of place-of-care manufacturing is a quick turnaround time with fresh leukapheresis cells and fresh final cell product for onsite patient infusion without cryopreservation. However, lot release testing takes time in order to confirm identity, safety, purity and potency. The traditional centralized laboratory approach may not be suitable for the decentralized place-of-care lot release testing purpose. Quick turnaround time for lot release testing is essential for a place-of-care manufacturing strategy. Traditional testing methods take too long to release the product without cryopreservation. Equivalent rapid test methods can and have been developed. Examples include rapid sterility test methods and

PCR based mycoplasma testing. Perhaps the most challenging part of lot release is biological potency testing which is often complex and time consuming. Were validated rapid tests available, the time for testing could be reduced significantly, but only to a certain degree. It still might not be quick enough for a timely release of fresh cell products. One possible solution to this is to use in-process testing and monitoring to conditionally release the final product in real time while the full lot release testing can be used for retrospective confirmation with an action plan in case some test results from the full lot release testing happen to be out of specification. This approach will likely require a new regulatory mindset and calls for innovative regulatory approaches.

Assay validation is an essential part of a BLA submission package. If lot release tests are performed locally at place-of-care sites, a common master assay validation protocol is certainly needed to ensure all local labs perform the tests the same way with the same instruments and devices. If in-process tests and controls are to be used in place of the final product release testing, we must also create an appropriate path for assay validation.

Pre-license inspection (PLI) of manufacturing facilities is an essential part of the BLA review and approval process (Section 351 of the Public Health Service Act (PHS Act) and section 704 of the Federal Food, Drug and Cosmetic Act (FD&C Act) and 21 CFR 601.20). For traditional centralized manufacturing setting, the FDA will inspect the main manufacturing facility for the final CAR-T product and perhaps another facility for critical components such as a viral vector. However, in the decentralized manufacturing setting, the PLI would present a logistical challenge for both the FDA and the manufacturer. Multiple inspections would be required to ensure all the manufacturing sites are compliant with the CGMP requirements. This may require new inspection approaches. FDA has gained experience in inspections during COVID-19 pandemic. Virtual inspections, extensive paper reviews and engagement of local inspectors are great options. One essential procedure requirement for biologics manufacturing and FDA inspections is the FDA Establishment Identifier (FEI#) and DUNS# for the place-of-care manufacturing units. Sponsors/applicants need to ensure these numbers are pre-registered with appropriate authorities.

The above manufacturing related issues are not an exhaustive list but do represent key points that need to be carefully considered when planning to set up decentralized place-of-care manufacturing facilities in a hospital setting. Based on current analysis, these issues seem to be solvable in practice, especially given that the manufacturing process itself is a closed and automated system. We expect that experience during actual clinical studies will provide further supporting evidence that the decentralized manufacturing approach may be more robust with shorter vein-to-vein times and vastly improved cost effectiveness.

We encourage manufacturers to interact with the appropriate FDA review division to have an early dialogue and proactively discuss potential issues that could become major deficiencies in the BLA package. One could initiate this dialogue with the FDA as early as at the end-of-phase 2 meeting but definitely no later than at the pre-BLA meeting. These issues discussed in this whitepaper should help readers to map their own plans in pursuing the path of place-of-care manufacturing for cell therapies.

In order to realize the full potential of the place-of-care manufacturing approach, a world-wide network treatment centers with such capability should be established. This would be especially beneficial to areas where a high-cost centralized manufacturing facility is not feasible. As an integral part of this effort, global regulatory authorities would need to participate and create a suitable regulatory pathway to oversee this novel manufacturing setting. To that end, recently (12 August 2021) the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) initiated a public

consultation for a proposed regulatory framework of "Point of Care manufacturing" (POC) (equivalent to the concept of place-of-care manufacturing in this whitepaper) for medicinal products that have very short shelf lives and/or highly personalized including cell and gene therapies (https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing). The proposed regulatory framework appears to cover a broad spectrum of products at different development stages from clinical trials to market authorization. The main objective is to establish a regulatory framework for rapid decision making on product critical quality attributes for quick on-site product release while maintaining the product's safety, purity, quality and potency. The proposal does touch upon some detailed concepts such as establishment of a "*system of local verification based on compliance of equipment against qualification criteria, the process against validation criteria, materials against pre-defined attributes and the manufacturing process against key process criteria…*" and retrospective lot release testing after dosing.

It is our hope that manufacturers and sponsors will work with the FDA here in the US with other regulatory bodies world-wide to formulate similar regulatory frameworks for place-of-care manufacturing to facilitate the rapid development of personalized therapies that reach a wider patient population.