Meeting Summary of the 20th Cell Therapy/FDA Liaison Meeting
[Not FDA Reviewed or Approved]

December 8, 2023
Virtual Meeting

Host Organization:

International Society ISCT Cell & Gene Therapy®

Participating organizations: **AABB, ASFA, ASTCT, CAP, CBA, FACT, FDA/CBER/OTP/OCTHT/OGT/OCBQ/OCOD, ISCT, NHLBI, NMDP, SITC, USP, WMDA**

The FDA CTLM Meeting was held on December 8, 2023, from 1:00 – 3:00 pm ET. After opening remarks from the ISCT North America Legal and Regulatory Committee Designate, Olive Sturtevant, MHP, MT(ASCP)SBB, SLS, CQA(ASQ), and Director of FDA **Center for Biologics Evaluation and Research (CBER), Peter Marks, MD, PhD,** the meeting commenced.

PRESENTATION 1: Cellular and Tissue Material as Raw "Starting" Material for iPSC clinical products and other Cell Banks – Laura Ricles, PhD

Dr. Ricles' presentation focused on donor eligibility requirements for cell products' starting material.

According to CFR §1271.45(b) Donor Eligibility (DE) determination is required for all donors of HCT/Ps (except as provided under section §1271.90) through donor screening and testing for relevant communicable disease agents or diseases (RCDADs). In the case of an embryo or cells derived from an embryo, a DE determination is required for both the oocyte and semen donor. As described in subpart C, 21 CFR part 1271, donor screening and testing are required to reduce the risk of transmission of communicable disease agents and diseases, including risk associated with xenotransplantation.

Donor screening and testing for infectious agents, on the other hand, are required when the product source material is from *allogeneic* human donors (e.g., tissues, cell banks, cell lines, etc.). Through a rule that went into effect on May 25, 2005, FDA has stipulated the details such as what must be tested and when, what methods and kits must be used, and how they are tested and by whom.

However, there are certain cells in which DE determination is not required such as:

- Cells and tissues for autologous
- Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use

- Cryopreserved cells or tissue for reproductive use, other than embryos, originally excepted under §1271.90(a)(1) or §1271.90(a)(2) at the time of donation, but subsequently intended for directed donation with a condition that, *additional donations are unavailable* **and** *appropriate measures are taken to screen and test the donor(s) before transfer to the recipient*
- A cryopreserved embryo, originally excepted under §1271.90(a)(2), that is subsequently intended for directed or anonymous donation, when possible, appropriate measures should be taken to screen and test the donors before transfer to the recipient

Furthermore, according to CFR 1271.155, an exemption from or alternative to any donor screening and testing requirements as described in subpart C (donor eligibility) or D (current Good Tissue Practice) may be requested to FDA. This request must be accompanied by supporting documentation including all relevant valid scientific data and *either* a justification of the requested exemption *or* a description of a proposed alternative method of meeting the requirement.

In the discussion, a question was raised about the donor screening and testing requirements for cells and tissues collected for research and process development purposes (i.e. IND). It is currently unclear for the investigators whether donor screening and testing for infectious disease are required or not given the cell type (i.e. *autologous*) and it is not collected or handled under the GMP or GTP conditions. The stakeholders suggested that clear guidance would be appreciated to clarify this confusion.

Another question was raised to clarify which guidance should the stakeholder use in blood banks and transfusion environments which was then clarified by the FDA that any products containing HCTPs must follow CFR 1271.

The FDA recognized that this remains a challenge for the stakeholders therefore during the IND review, FDA always requests as much information as possible on the cell manufacturing process such as whether GMP or GTP process was followed, what type of reagents were used, etc. It is also realized that the extent of information that the applicants can provide is varied, therefore it is highly recommended for the applicants to discuss their IND applications with the FDA before submitting.

In addition, the FDA is currently working on revising the 2007 Donor Eligibility Guidance for HCTPs, the stakeholders are therefore encouraged to keep out and reach out in case there are further questions.

PRESENTATION 2: Changing the definition of starting material – Rebecca Gardner, MD

Dr Gardner's presentation focused on any *autologous* where cells are obtained from MNC collection and then manufactured.

According to the FDA Draft Guidance on Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products (March 2022) the starting material for manufacturing begins at the time of collection of cells. This aligns with a definition described under another FDA Guidance on Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (January 2020).

This definition, however, creates more challenges for the sponsors not only from the oversight but also from the logistical perspective, especially in a multi-center clinical trial setting. This would mean each clinical site must have SOPs for all steps (patient selection, cell collection, processing, labeling, and

shipment). Given the number of products handled by the site, variation between products is likely to produce errors and prohibit the utilization of apheresis products for multiple distinct products in the future. Impacts on Centers include the extensive amounts of quality agreements, technical/business agreements, audits, and FTE required to execute this process.

Dr Gardner proposed a new approach by increasing the role of accreditation agencies in bridging the gap between collection sites and cell therapy manufacturers. If the apheresis is treated as a clinical procedure and removed from the manufacturing process, the manufacturing responsibility could start from the time that the cells are received rather than at the time of collection. This approach will align with how DLI and HPCs are handled for minimally manipulated products.

If this approach was implemented, the collection of cells (*leukapheresis*) procedure would need to be standardized with the help of accreditation bodies such as FACT, AABB, or CAP. Through this approach, the audit responsibilities can then be delegated and centralized. Dr. Gardner also highlighted some audit programs currently offered by NMDP and FACT that can support this approach.

In the discussion, the FDA clarified that according to the FDA guidance, the manufacturing process starts when the material is received and not during collection (*apheresis*). However, for the BLA application, to ensure the quality of the starting material is maintained, the apheresis site is required to have a defined procedure for the starting material used for the product.

PRESENTATION 3: QC Testing for Point of Care (POC) Manufacturing – Patrick Hanley, PhD

Dr. Hanley began his presentation by highlighting some facts that indicated the increased interest in point-of-care manufacturing.

- The number of sessions (3) dedicated to discussing this topic:
    - 2 sessions at the ISCT 2023 Annual Meeting in Paris (May 2023)
    - 3 sessions at the ISCT 2023 NA Regional Meeting in Houston (September 2023) including a plenary session featuring Dr. Kimberly Schultz from the Office of Gene Therapy CMC (OGT), CBER-FDA.
- A discussion paper issued by CDER: Distributed Manufacturing and Point-of-Care Manufacturing of Drugs in October 2022.
- The number of companies looking to enable POC manufacturing (Orgenesis, Lonza, Miltenyi, aCGT Vector, others)
- Although *Hospital Exemption* in some European countries is not necessarily point-of-care manufacturing there is an interest in performing point-of-care manufacturing in a hospital setting.

Dr. Hanley also highlighted the interest in using automated manufacturing technologies such as Prodigy, Cocoon, Sepax, Rotea, etc. to manufacture complex CGT products. Some research centers have been using these technologies for a while.

POC manufacturing, however, creates significant challenges such as:

- Comparability and consistency between sites
- Availability of trained workforce

- Transfer knowledge between sites

Although the use of automated manufacturing technologies will be able to mitigate most of these challenges, the advancements in QC testing in the last 10 years have been limited. The only significant advancement in QC testing is cell counting, while others are insignificant.

The advancements in QC testing would not only enable POC manufacturing but also reduce the need for a specialized workforce to perform complex QC assays, the variability between sites, turn-around time, false positives (especially for sterility tests), etc.

At the end of his presentation, Dr Hanley highlighted a few scientific publications that show the use of AI and Machine Learning to better utilize and analyze the available data. A workflow was shown to simulate how automation can potentially better predict manufacturing outcomes and accommodate rapid manufacturing in the future.

Given the continued interest in the POC and the potential for automated manufacturing technology (i.e. QC testing), it is suggested for the FDA to:

- Continue to engage and learn about the potential for POC
- Recognize the momentum of POC manufacturing
- Recognize that QC testing remains a bottleneck and unmet need in CGT
- Consider future RFPs addressing the unmet needs related to QC tests for cell & gene therapy
- Consider expanding work with USP and others to develop better test methods and standards for QC testing

During the discussion session, one of the stakeholders acknowledged that comparability is one of the biggest challenges in manufacturing, a better test method would be greatly appreciated especially in potency assay.

The FDA acknowledged that POC manufacturing and QC testing are important topics that are on their radar and appreciated the stakeholders' continued interest in this.

PRESENTATION 4: Request for Guidance Document Clarifying Which Entities are Required to Register with FDA for Manufacture of Human Stem Cells, HCT/Ps – Patricia M. Kopko, MD

Dr. Kopko's began her presentation by outlining the regulation of HCT/Ps under section 361 of the PHS Act, including cells that are minimally manipulated and intended for homologous use. Some HCTPs, however, are exempted such as:

- The combination of the cells or tissues with another article except for water, crystalloids, or a sterilizing, preserving, or storage agent, and the HCT/P does not have a systemic effect or has a systemic effect and is for autologous use, is for allogeneic use with a first or second-degree blood relative or is for reproductive use.
- The HCT/Ps are used solely for nonclinical purposes or if they are used in the same individual during the same surgical procedure

Although the following FDA guidance, Same Surgical Procedure Exception under 21 CFR 1271.15(b) and Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, has helped clarify the exceptions and contain helpful examples, confusion remains regarding the interpretation of **homologous use** and **more than minimal manipulation**. Experts in the field continue to receive questions regarding whether an entity needs to register.

At the end of her presentation, Dr Kopko highlighted that the current published FDA Guidance for Industry on Biological Product Deviation Reporting for Blood and Plasma Establishments has been valuable to the blood community, similar guidance to cover the manufacture of human stem cells and HCT/Ps would be highly valuable to the cell therapy community.

In the discussion, the FDA clarified that resources to clarify the confusion are available on their website (see below), but they also realized that this is a concept that is difficult to grasp, therefore the suggestion will be taken into consideration.

- Federal Register: Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs, https://www.federalregister.gov/documents/2016/08/31/2016-20471/requirements-for-foreign-and-domestic-establishment-registration-and-listing-for-human-drugs
- Tissue Establishment Registration, https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/tissue-establishment-registration
- Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal
- Electronic Drug Registration and Listing System (eDRLS), https://www.fda.gov/drugs/guidance-compliance-regulatory-information/electronic-drug-registration-and-listing-system-edrls

PRESENTATION 5: Challenges with Moving Cell and Gene Therapies into the Commercial Space for Rare Diseases – Kevin Bosse, PhD, RAC-US, CABP(H)

Dr. Bosse started his presentation by highlighting that CGTs offer unique and distinct advantages to '*conventional*' therapies and provide a truly curative option. More and more clinicians are interested and believe that these modalities could help their patients.

Surprisingly, rare diseases have affected approximately 25-30 million individuals. It might be individually or specifically '*rare*' but when taken together, it is no longer '*rare*'. In addition, Citeline report shows that over 1200 cell and gene therapy product development programs are for rare diseases.

Dr. Bosse acknowledged that the FDA plays an important role in the growth of CGT space. Despite the great programs/initiatives that FDA has such as the reorganization of OTAT into OTP, operation Warp Speed, Bespoke Gene Therapy Consortium, and FDA designations, the following challenges remain:

- The current market seems to be viable at approximately 100 treatments/year for gene therapies (even less for rare diseases)

- The global financial situation has influenced the investor decision to fund the CGT product development (i.e. rare diseases)
- Very active and well-connected patient family foundations can do a lot but the size of the foundation and the number of resources that are varied limit their ability to do more.
- The INDs sponsor tends to abandon the program if it does not have the outcome that they are looking for or if there are no commercial dollars in it

At the end of his presentation, Dr Bosse shared some of the regulatory burdens in putting the rare disease programs forward.

- The current FDA efforts can be further streamlined to lower the regulatory burden and make the disease programs commercially available
- The current nature of ultra-rare disease (N=1) will not allow products for such diseases to have a BLA
- The goal in all drug development is a lawfully marketed commercial product, but what if that isn't currently viable for a specific disease?

In the discussion, the concept of perpetual INDs for ultra-rare diseases was discussed. Although the concept is potentially a good solution, it might lead to complexity in the long run especially when the principal investigator moves to another institution.

The FDA ended the discussion by acknowledging that this topic is something that they are interested in and thinking of and appreciated the stakeholders in organizing the meeting.