

FINAL Meeting Summary of the 15th Cell Therapy/FDA Liaison Meeting

March 5, 2019

Bethesda, MD

Host Organization:



Participating organizations: AABB, ASFA, ASGCT, ASH, CBA, FACT, FDA/CBER/OTAT/OCD & OCOD, ISCT, ISSCR, NHLBI/NIH, PACT, SITC, USP

The FDA CTLM Meeting was held on March 5, 2019 from 12:30 – 3:30 pm. The following topics were presented during the meeting with the agency. After a welcome from the ISCT North America Legal and Regulatory Committee Designate, Olive Sturtevant, the meeting commenced.

PRESENTATION SESSION 1: Regulation of Biobanking Material for Future Products

- [Presentation 1](#): *Mahendra Rao, MD, PhD (ISSCR)*

Dr. Rao discussed the unique attributes of banked autologous products and shared various models of other biobanked material. In practice, each lot of autologous cells is processed by different groups using different procedures. When using these banked cells as starting material in a clinical trial, it is hard to consider them as key raw materials in the context of a standard model given that different cell banking facilities use variable banking practices. In the absence of guidance, cell banks and previously banked products prepared, cryopreserved and stored for various applications are now available as starting material for new purposes such as starting material for new products. Recent advances suggest that gene editing may enhance the utility of these banked cells. Those storing the cells are not the ones filing for an IND to use them. These cell banks can include bone marrow from cadaveric donors, expanded bone marrow, placental cell products, iPSC banks, etc. There are unique issues associated with biobanking and these banks if used for sourcing raw material intended for clinical use should be regulated. As previously described, each lot is a single source of raw material and is then processed by different groups with different procedures for a variety of potential trials and indications. In some situations, previously collected clinical products under an IND approved for a single indication are now cells being used for multiple additional indications. What happens to units that are stored? What happens to autologous processed cells? The biobanked cells are the starting material. Dr. Rao has suggested that biobanks which supply processed samples need to be regulated and draft guidance documents be developed. Dr. Rao has

asked if the FDA can advise on how they expect biobanks to be regulated and asking if the FDA considers state licenses for establishing a banking facility akin to blood banks to be sufficient. Comparability by end products should be considered. Autologous processed cells should be treated somewhat differently than allogeneic processed cells and these differences should be clarified. Dr. Rao asked for the FDA to consider harmonizing state licenses for establishing a banking facility akin to blood banks and also, to consider a role for accreditation organizations.

Group discussion ensued with a participant adding a category to consider: banked research samples which could potentially be used for a cell product's starting material. FDA staff expressed appreciation for the presentation and perspective but is unable to comment on items that may be in progress within the Agency. The quality of the starting material should be reviewed on a case by case basis. During the discussion, the 2011 FDA guidance document was referenced, "[Current Good Tissue Practice \(CGTP\) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\).](#)"

Commentary then centered around the unique challenges of autologous products which are not fully addressed in the document. Regarding the state license request from Dr. Rao, FDA does not govern state law.

Opportunities for input could potentially include a journal article or even better, FDA staff reminded the group, would be the existing process to suggest guidance. It uses the public docket. The significant limitation in this setting is that there is no mechanism for the banking entity to interact with FDA, given the nature of products as starting material at the banking stage (not final products from sponsors). FDA commented that not all materials currently used in a biobank are necessarily qualified for use in clinical manufacturing for raw material. The FDA does expect that all raw materials used in clinical manufacturing to be qualified. FDA staff committed to making public presentations on related concepts when opportunities present and staff are available. The group encouraged FDA to use such examples as autologous T cells, Natural Killer (NK) cells, and cord tissue derived mesenchymal stromal cells (MSC). A mechanism for having these products reviewed (in the absence of a phase I trial in place) would be helpful. Attendees were also reminded of informal mechanisms for question answering (via professional organizations) or by email submission to industry.bioloics@fda.hhs.gov The role of drug master files (DMF) as a potential model was also discussed. Both INTERACT and pre-IND meetings could play a role with the DMF process though the INTERACT meeting platform is more appropriate for animal toxicity studies but could be used for asking questions and assessing the use of banked cells.

FDA staff also reminded the participants to look at the 1271 regulations and be mindful of GMP compliance with the expectation that compliance would likely be needed down the road for using these materials in a trial. Requests for exemption from the regulations is another potential approach. One attendee noted that over 50% of the companies in Japan cannot source these cells into the US even though the regulations appear more friendly on the periphery. Accrediting and professional organizations can also write papers for unofficial FDA review and/or publication. Dr. Rao noted that AABB had worked with the Agency on similar topics in the past and this model was successful.

PRESENTATION SESSION 2: Collection of MNCs for Immune Effector Cells

- [Presentation 2: Jay Raval, MD \(ASFA\)](#)

Dr. Raval discussed that the FDA approved two CAR T-cell products recently and that there are numerous ongoing clinical trials with Immune Effector Cells (IEC). Collection facilities are required to collect mononuclear cells (MNC) as the first step in obtaining the raw materials to produce either licensed products or IEC products. Apheresis sites experience the inconsistencies in procedures for the apheresis collection of MNC. The goals of apheresis in a clinical manufacturing context are to have a consistent, robust process optimal for the therapeutic product and ensure safety and comfort of the donor. For hematopoietic progenitor cell collections or donor lymphocyte infusions, most accreditation agencies (i.e., AABB, FACT) have standards requiring a written order to include goals of collections. This is not the case with many industry sponsors for collection of MNC for production of CAR T-cells and other IEC products. Some manufacturers simply recommend a wide range of total blood volume (TBV) to be processed at the time of collection. Regarding the pre-apheresis collection assessments for IEC, the collection protocol may not include an assessment of donor suitability or an assessment based on total nucleated cell (TNC) and/or CD3 pre-apheresis collection counts. This leaves room for interpretation and uncertainty for collection staff. There is no clear guidance on the collection formula to be used. Some centers may not be familiar with some of the calculations for calculating collection efficiencies. This is problematic because there is no certainty of obtaining appropriate numbers of target cells via apheresis and these cells are critical to the manufacturing process and therapeutic outcome. Different rules are applied at different centers. This along with not stating the target dose and population and just using x-blood volumes, can lead to collection of cells other than the target populations. Often, the targeted cell dose is not given, which leads to inconsistencies and product variability.

A range of TBV is typically requested for the collection. This creates its own inefficiencies as patients are kept on apheresis devices longer than needed just to ensure that “adequate product cellularity” is assured and this may pose an increased safety risk to patients. The goal should be to obtain the cell target and goal in fewest collections possible. Dr. Raval stated that these centers would like to see that peripheral count assessments specific to the product be mandatory prior to apheresis collection. This is to ensure ample starting materials for IEC production, to protect donors from unnecessary and/or prolonged collections and to prevent collection failures. Dr. Raval discussed that the desired outcome would require specific goals for collection of cells for production of CAR T-cells and other IEC products, e.g., number of cells needed to start a successful manufacturing process. Doing so will reduce variability in starting materials for IEC products; optimize quality of collections; enhance safety of our donors by eliminating unproductive collections, longer collections than necessary and collection failures; allow collection of products with optimal target cell counts and low presence of contaminating cells in a minimal volume.

During the discussion, the opportunity to decrease the failure rate of product collections was discussed. This could perhaps be addressed by instilling best practices, standards, etc. There needs to be a better effort to track product failures when related to the collection of the starting material. In an informal poll among some peers, at least eight different approaches for collecting the same product were shared. Additional discussion on the question of whether it is widely understood what the failure rate of these products might be, as most seemed, to be anecdotal. FDA staff noted that these are life-saving therapies and the issues raised are important things to think about. Additional variability is related to the patient disease state and treatment history. FDA and healthcare professionals are encouraged to watch for public meetings where these issues could also be raised. For facilities that are unable to sample, measure and calculate CD3+ cells, an optimal collection window could be missed. All factors contributing to product failure are not currently known. A lack of data metrics, or inputs, also limits the ability to standardize best practices. Professional meetings offer a venue for this discussion. Other variables such as the collection device, cryopreservation or other processing steps also add variability. Resistance to data sharing between sponsors further complicates the landscape. There may also be some opportunity to highlight and summarize product collection variability in IND report. Registry data can be problematic as not all variables are captured. Retention samples could also play a helpful role, potentially. A white paper might also contribute to starting the dialogue.

PRESENTATION SESSION 3: Minimum Characterization Criteria for Clinical Grade iPSC Products

- [Presentation 3](#): *Aisha Khan, MS, MBA (PACT)*

Ms. Khan opened by explaining that establishing guidelines for minimum characterization criteria is needed for induced pluripotent stem cells (iPSCs). A crucial problem in both the analysis of many human diseases and the development of effective therapies to treat disease is the incomplete understanding of the role played by human genetic variation in their development. She suggested that guidelines need to be established in the following areas: donor qualification in 21 CFR 1271, genetic testing; iPSC cell bank testing, iPSC final product testing. Challenges include iPSC derivation, such as safety and efficiency of the reprogramming method, donor-to-donor variability and choice of starting materials. Other iPSC challenges include areas such as the development of a cell culture system for iPSC generation and expansion, cell sensitivity and robustness, and cryopreservation and revival. Safety and Quality Control challenges can include normal karyotype, residual plasmid clearance, in-process controls to evaluate iPSC quality, critical attributes of the final products, and standard safety concerns such as sterility. iPSC technology has positive attributes to include eliminating ethical issues of embryonic cells and the donor's clinical phenotype is often known when working with iPSCs. Challenges of working with iPSCs include that cells would still have genetic defects; one of the pluripotency genes is a cancer gene, viruses (used in the mfg process) might insert genes in places we don't want them (causing mutation); for iPSC cells to become effective treatments will likely require the donor's cells to undergo genetic alterations (will the donor have been properly consented / be fully informed of this possibility)? Longer term consequences which are still unknowns include the fact that iPSC technology include

genetic defects (either undetected or detected but with unknown impact) that could affect recipients and that the act of reprogramming itself could create altered or carried genetic defects at some point in the future. Additional questions to consider when banking / using iPSCs include considering how donor age influences the reprogramming process and iPSC functionality? Is there a way to perform genetic testing to determine this impact? Differentiation potential is important to the utility of iPSCs. In vitro differentiation assay(s) exist to try and answer this question. These assays are used to (a) confirm the differentiation potential of iPSC through spontaneous differentiation and formation of the Embryoid body, (b) to analyze differentiation for the presentation of the markers of cells of the 3 germ layers, by qPCR of the Embryoid body. iPSC genome can reproduce that of the cell from which they are derived. iPSCs can potentially develop genetic abnormalities during reprogramming or prolonged cell culture. iPSC genome integrity needs to be routinely monitored by an appropriate method (karyotyping commonly used). Dr. Khan suggested the future possibility of exploring the use of single-cell RNA-seq to identify unique subpopulations that are especially suited for a patient-specific therapy. In conclusion, using autologous or allogenic iPSCs has advantages and disadvantages, and the choice of appropriate strategy may vary depending on the intended use. Additionally, there remain many factors that affect establishing transplantation therapy using iPSCs. To avoid tumorigenesis and establish effective differentiation into the intended cells, further investigation is needed to clarify which iPSC line is the most suitable and how these lines can be best selected.

It was discussed that autologous products do not require donor eligibility, but it is encouraged. Cells destined for allogeneic use must include a donor eligibility step. One could do compendial adventitious viral testing as needed. The general discussion focused on the bank type and what the stored product “becomes.” Test methods should not be mandated as techniques and targets could vary. For compendial testing, there are few validated suppliers of these tests (for example, species-specific, endogenous/adventitious viruses) and it could require a lot of test article to complete a testing panel (average master cell bank, MCB, may be 300 vials) as a large amount is needed for viral tests alone. For shipment with viral testing, issues were discussed with having to repeat viral testing when products are sent from one GMP facility to another. Other issues raised included the concerns with expanding a MCB indefinitely. If the product is transferred to another facility, would all testing need to be repeated? Clarification on this topic would be helpful. Working cell banks (WCB) have yet another testing requirement and the level of testing is different. One model could qualify the cell bank based on exposure risk during the shipment. A DMF could also be used in this case but keeping it updated and current can be a challenge. The WCB could be considered a raw material. Stakeholders do not often think of them as raw materials because of the HCT/P regulations. A DMF could be cross referenced so that everything does not need to be repeated. FDA staff noted that when cell lines are passed around in clinical production, everyone assumes the testing was done but if documentation to this effect cannot be produced, then testing needs to be performed. Need to look at karyotyping periodically over time while in culture as there can be both additional mutations and epigenetic variability.

PRESENTATION SESSION 4: Early Interaction Mechanisms for Tool/Device Developers

- [Presentation 4](#): *Michael Mendicino, Ph.D. (ISCT)*

Numerous product developers, at both preclinical and clinical stages of development, desire (and often require) the use of innovative tools, ancillary materials, and manufacturing-enabling equipment in their OTAT-regulated product intended for the IND through BLA pathway. These innovative tools, ancillary materials, and manufacturing-enabling equipment (herein referred to as novel technologies) are not usually regulated as drugs, biologics, or medical devices, so their application in CMC/investigational medical product development are reviewed in the context of the product developer/sponsor IND. Often these novel technology manufacturers are in the “unknown zone” between prototype and customer utilization in investigational medical product manufacture for a clinical trial under IND. Generally, these novel technologies are not regulated other than in the context of an IND. These novel technologies may be developed by one manufacturer for use in many different manufacturing processes for therapeutic products (i.e., cell sorting as compared to cell analysis, culture media as reagent compared to excipient, etc).

For a novel technology manufacturer that does not have an internal R&D program of their own, the following occur:

- don't understand what the FDA requires for their novel technology that product developers want to/will use in their cGMP-compliant drug product manufacturing process, including both IND and commercial stages of development;
- have proprietary technology that they can't/won't share with product developers for INTERACT, pre-IND and/or IND, or the public, in order to protect their IP (e.g., trade secret), that is assumed to be needed for IND review;
- have little experience with FDA regulatory filings;
- heard of the Master File process but don't know how it applies to their technology, or how to utilize the Master File process.

For a product developer/IND sponsor, the following occur:

- use of novel technology benefits or is even required for their investigational medical product development to promote (more) favorable preclinical safety/bioactivity profile;
- wants more information from the novel technology manufacturer that manufacturer does not want to provide as info is considered confidential (e.g., trade secret);
- does not want to include novel technology manufacturer in their INTERACT and/or pre-IND meeting(s) in order to protect their own IP (e.g., trade secret).

FDA interactions currently permitted with OTAT prior to IND submission includes [INTERACT meeting](#) and the product developer can request a formal [Type B pre-IND meeting](#). *[This statement is now outdated.]*

Program is now available through the CATT at CBER : <https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt>]

Currently, the novel technology manufacturer can submit a Master File. No guidance on format, which is very novel technology-specific. Draft FDA Guidance [“Chemistry, Manufacturing, and Control \(CMC\) Information for Human Gene Therapy Investigational New Drug Applications \(INDs\)”](#) is currently available. This draft guidance mentions Master File is required to be eCTD-compliant only. Currently available eCTD Guidance, “Commercial Investigational New Drug Applications (INDs) and Master Files must be submitted using eCTD format”

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>”.

Potential suggestions include:

- possibly incorporating relevant Guidance language into the Draft FDA Guidance “Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (IND)”;
- develop separate Guidance that covers all in-scope novel technologies;
- OTAT Learn session on novel technology-specific Master File structure.

Potential suggestions for early FDA CMC interaction includes: modify scope of INTERACT to include novel technology manufacturers; allow pre-Master File or “Early Manufacturing Technology ” interaction as an exclusive option outside of INTERACT but using a similar SOPP for CBER; allow novel technology manufacturers the opportunity to reach out to CBER OTAT via RPM Team to request CMC reviewer for very limited, informal advice, based on reviewer bandwidth and expertise (that staff member could be the intended assigned reviewer for the subsequent Master File). *[This statement is now outdated. Program is now available through the CATT at CBER : <https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt>]*

FDA staff also shared that the broad buckets of novel technologies are very different and that once the concept of the novel technology in a specific product manufacture is developed, there is a clearer path for review. Manufacturing controls are key. For example, if a non-medical grade device is used, such as a centrifuge, this could be acceptable if all aspects of the process are under complete control. A Master File would not be needed for a simple piece of equipment, depending on the application. Something like a gene-expressing vector that becomes part of the drug substance may require more documentation than some other ancillary materials. There is also a role for Certificate of Analysis review by the sponsor since not everything in a DMF can be qualified. The basic foundation is helpful to understand. These meetings help identify gaps and needs for additional education. These questions should be included in pre IND meetings. Quality agreements and critical quality attributes are also important.