

FINAL Meeting Summary of the 14th Cell Therapy/FDA Liaison Meeting

January 30, 2018

Bethesda, MD

Host Organization:



Participating organizations: AABB, ABC, ASGCT, CBA, CIBMTR, FACT, FDA/CBER/OTAT & OCOD, ICCBBA, ISSCR, ISCT, NHLBI/NIH, PACT/EMMES, USP

The FDA CTLM Meeting was held January 30, 2018 from 12:30 – 3:30 pm. The following topics were presented during the meeting with the agency. After a welcome from the ISCT NA LRA Designate, Olive Sturtevant, the meeting began.

PRESENTATION SESSION 1: COMPARABILITY OF iPSC LINES FOR A MASTER CELL BANK

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

Historically, the FDA has addressed comparability issues related to biological products by asking sponsors for data from actual clinical studies, *in vivo* preclinical studies, historical data, and *in vitro* data. With the advent of a wide variety of novel regenerative medicine products, comparability becomes a complicated issue.

Autologous pluripotent products are especially challenging as a single line of iPSC can be used to generate many products. Not only is the cell type critical, but there are multiple iPSC therapy models including autologous, one donor to many recipients, and many donors to many recipients (HLA matched). Suggestions were made for FDA to consider how cell banks have been previously used for biological product manufacturing, as well as defining the process for replacement at MCB stage and final release criteria. A request for a white paper or guidance for the industry was put forth to allow the current models of therapy to be implemented with clarity and to integrate well with previously approved products. It would be of particular importance to adult stem cells and allogenic small-scale manufactures where intermediate working banks are made. Following the meeting, Dr. Rao provided the following references: 1) Rao, MS & Atala, A. “[Developing Induced Pluripotent Stem Cell-Based Therapy for the Masses](#)” 2) Carpenter, MK & Rao, MS. “[Concise Review: Making and Using Clinically Compliant Pluripotent Stem Cell Lines](#)”.

PRESENTATION SESSION 2: CHALLENGES IN CAPTURING LONG TERM FOLLOW UP OF RECIPIENTS OF GENETICALLY MODIFIED CELLS

- [Presentation 2](#): *Marcelo Pasquini, MD, MS (CIBMTR)*

M. Pasquini reviewed the history of the CIBMTR and the mandate to collect data on hematopoietic cell transplant patients. In Summer 2016, CIBMTR launched the Cellular Therapy Essential Data (CTED) forms in FormsNet, an electronic data collection system. The cellular therapy registry data flow includes the following forms. Multiple timepoints are captured as per the table in the presentation. Of particular concern to the stakeholders is how to reduce the burden on data collection and reporting, especially when there are multiple treatments and treatment centers. Issues pertinent to cellular therapy follow-up (15 years) are to optimize follow up and patient tracking through electronic Patient Reported Outcomes (ePRO) platform. For those patients who become pregnant, there are outcomes forms to capture pregnancies after CT and outcomes. What level of follow-up is necessary to ensure safety? Discussions with multiple companies and investigators to address these issues result in wide variability in plans, with variation in burden anticipated for centers treating these patients. There needs to be a middle ground with collection of essential data while minimizing burden.

Conclusions and recommendations for the FDA to consider: 1) A standardized database will be important to the field, which will avoid having multiple databases for each sponsor/company and for similar products. 2) Recommendation of minimal follow up schedule to avoid increasing the burden of data collection and maximizing efficiency. 3) Promote innovative approaches for patient tracking and follow up.

PRESENTATION SESSION 3: RMAT DESIGNATION UPDATE

- [Presentation 3](#): *Wilson Bryan, MD, (FDA OTAT)*

W. Bryan presented an update on the Regenerative Medicine Advanced Therapy (RMAT) Designation. Specifically, Section 3033 of the 21st Century Cures Act has the definition of Regenerative Medicine Therapy (RMT) which includes cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act. The FDA interprets this to include certain gene therapy products as well. A drug is eligible for RMAT designation if: it is a regenerative medicine therapy; the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.

Receiving RMAT designation does not mean the product is approved for marketing, it means the product has received the RMAT designation. The sponsor can make a request with a new IND submission or as an amendment to an existing IND. View this website for additional information:

<http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm> The FDA has 60 calendar days to determine if designation criteria are met, will provide a written response and if not granted, FDA will provide a written description of the rationale.

There are benefits of RMAT Designation, which include: Interactions with FDA to expedite development and review of regenerative medicine advanced therapies. Benefits available to breakthrough therapies including early discussions of any potential surrogate or intermediate endpoints to support accelerated approval. Additionally, sponsors may be eligible for priority review and/or accelerated approval.

Dr. Wilson Bryan, CBER/OTAT summarized RMAT designation requests as of Jan 28, 2018:

- Status: 15 approved, 22 denied and 6 pending
 - Reasons for RMAT denial: administrative reasons such as an inactive IND or no preliminary clinical evidence submitted, CMC (product is not comparable to the one used in clinical evidence), insufficient or improper preliminary clinical evidence.
- Specialty: 3 orthopedics, 4 oncology, 5 immunology, 7 cardiovascular, 10 neurology, 14 others.
- Applicant: 35 commercial and 8 academic.
- Product type: 23 CTs – allogenic; 14 CTs – autologous; 6 other
- Patient population: 36 requests for adult, 7 pediatric.
- Current study status: 20 in Phase II, 14 in Phase III and 9 in Phase I.

PRESENTATION SESSION 4: LICENSING OF CORD BLOOD UNITS FOR INDICATIONS OTHER THAN CURRENTLY APPROVED

Presentation by:

- [Presentation 4: Joanne Kurtzberg, MD \(CBA\)](#)

There are over 300 clinical trials for regenerative medicine applications with umbilical cord blood (UCB), other than hematopoietic stem cell transplant (HSCT). Clinical trials are occurring in babies with Hypoxic Ischemic Encephalopathy (HIE), children with cerebral palsy (CP) and adults with acute ischemic stroke. Favorable safety profiles and encouraging results in autism and CP. Both autologous, related and unrelated cord blood units are being utilized. The mechanism of action using cord blood in these patients is that cord blood acts through paracrine signaling to instruct endogenous cells to repair damaged tissue and to build new connections in the brain. Both autologous and allogenic units are under investigation. Eligibility is limited to patients without genetic causes of their disease. Patients with a PMH of cancer, immune deficiency, autoimmune disease, immunosuppressive or chemotherapy are ineligible. Patients treated with other cellular therapies are excluded.

Potential pathways to approval are problematic. Is it a 361 pathway? Then CD14+ is the active cell type by causing a paracrine effect. Is it a 351 pathway? Then conduct a trial, either single arm, open label phase III to confirm observations in phase II or conduct a randomized, multicenter, phase III study. This confusion impacts thousands of patients. If a BLA is required, who is responsible for obtaining the BLA? There is currently no guidance for private banks that have manufactured these products and it is not practical for each bank to get its own BLA. Is there a role for shared BLA, for those institutions that are not interested in licensing the product but do want to have safe product where therapies are available? Also, of concern is the application of the homologous use definition. A CBU is not a homogenous product, instead comprising of a variety of cells, each with their own native purpose. The recommendation in this case is to think of the CBU as a group of cells, with multiple homologous uses.

PRESENTATION SESSION 5: HUMAN PLATELET LYSATE REQUIREMENTS FOR CELL THERAPY EXPANSION IN SUPPORT OF CLINICAL TRIALS

- [Presentation 5](#): *Rob Tressler, PhD, MS (ABC)*

cGMP manufacture of cell therapies should avoid the use of non-human animal supplements. Current options include defined media, AB serum and human platelet lysate (HpL). Defined media has limited utility to date while AB serum is not optimal for culture of some cells and has supply concerns. This leaves HpL, which has extensive literature demonstrating its utility for cell culture. Multiple companies/organizations are marketing or developing HpL product formulations, however, variability exists in the manufacture of HpL, Therefore, it is essential to establish a minimum set of criteria for HpL production/characterization.

Starting material typically collects expired platelets for transfusion – collected at AABB accredited facilities and may be manufactured by facilities that are AABB and/or FACT accredited and that follow state and CFR guidelines for clinical blood products. A Certificate of Analysis (CoA) should be included with each HpL manufacturing lot. A stability plan may be needed to determine shelf life of HpL products for a specific storage condition. An *in vitro* cell proliferation potency assay can be used to support stability studies and HpL lot release criteria.

Suggestions for FDA to consider –

- A draft guidance for sourcing platelets that are the starting material for HpL production.
- Transfusion-grade platelets sourced from cGMP facilities with appropriate accreditations, Consent and Quality oversight.

- A cGMP compliant HpL manufacturing process preferred with Quality program oversight supporting environmental, equipment, personnel and materials management.
- A CoA with each manufacturing lot of HpL having the minimum criteria of sterility, protein concentration, IDM, endotoxin, mycoplasma, lot number, expiration date, additives (if used).
Optional: Growth factor(s) content, potency assay results.