Meeting Summary of the 16th Cell Therapy/FDA Liaison Meeting
[Not FDA Reviewed or Approved]

November 21, 2019
Bethesda, MD

Host Organization:

Participating organizations: **AABB**, **ASGCT**, **CAP**, **CBA**, **FACT**, **FDA/CBER/OTAT/ & OCOD**, **ISCT**, **PACT**, **SITC**, **USP**

The FDA CTLM Meeting was held on November 21, 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: Exclusion of Maternal Donors with Positive Screening but Negative Confirmatory Infectious Disease Testing Results, Impact on Public Cord Blood Banking

- ***Presentation 1: Joanne Kurtzberg, MD (CBA)***

Dr. Kurtzberg discussed that maternal donors of umbilical cord blood are screened and tested, as surrogates, for infectious diseases that are transmitted through blood by CLIA approved donor screening labs. Currently, if the donor is tested positive, the cord blood unit is deemed ineligible for banking or banked as an ineligible donor. Units from ineligible donors cannot be distributed under BLA. It was noted that maternal blood during or shortly after pregnancy have shown higher rates of false positive results in screening tests. Furthermore, the majority of mothers who screen positive for certain viruses have negative confirmatory tests. As such, it was requested that the FDA consider allowing banking and distribution of cord blood units with positive screens and negative confirmatory tests as eligible donors under the banks' BLA. Dr. Kurtzberg provided the example of the Carolinas Cord Blood Bank (CCBB) and reviewed the donor qualifications for banking, types of consent, screening process, and follow-up to check on the status of the child's health. Based on infectious disease exclusions from screening tests, 1-5% of otherwise eligible units are excluded based on non-Zika exclusion criteria Additionally, 10-25% of united of otherwise eligible units are excluded based on Zika travel risk exclusions. In 2019, only 20% of cord blood units collected at the CCBB met donor specifications for banking.

Several papers were cited, supporting high false positive rates or high rates of indeterminant results in samples from pregnant women, as well as studies attributing false positives to non-specific proteins and cross reactivity seen more frequently in pregnant women.

Dr. Kurtzberg ended the presentation with the following recommendations:

- Obtain travel histories for both the baby's mother and father
- Test all mothers with Zika NAT as part of donor screening and donor testing
- Confirm normal physical exam, especially the lack of microcephaly, on newborn physical examination
- For donors with travel risks, obtain a 1-year post donation follow-up to confirm normal child development and no suspicion of Zika infection
- If follow-up indicates no sign of Zika infection, the donor should be eligible, unit licensed, and NCBI eligible
- Continue screening and testing of all maternal donors
- When a donor has a positive screen for HBC, HTLV I/II, or HIV with a negative confirmatory test, allow banking and distribution under licensure
- When there is a travel risk associated with Zika but testing is negative and a 1-year follow-up on the mother and baby is normal, allow banking and distribution under licensure.

Group discussion ensued regarding donor testing methods. Dr. Kurtzberg clarified that screening vs. confirmatory tests are different; confirmatory tests are usually conducted through PCR. It was also noted that a false positive screen will continue to show as a false positive through repeated screens. Additional data from other centers were not presented during the meeting however it was discussed that rates are similar, and Hep B Core and HTLV I/II appear to be the most problematic for false positive screening. The group discussed that similar false positive screening results are also an issue outside of cord blood. It was suggested that a paper be developed to address this topic with additional data from other centers included.

PRESENTATION SESSION 2: Regenerative Medicine Advanced Therapy (RMAT) Update

- ***Presentation 2: Wilson W. Bryan, MD (FDA)***

Dr. Bryan discussed the wide range of OTAT-regulated products including gene therapies, stem cells/stem cell-derived therapeutic vaccines and cellular immunotherapies, combination products, devices and tissues. IND submissions for cell therapy products have grown significantly over the past 10 years with 154 submissions received in 2018. The total number of INDs have nearly doubled from 2016-2018, following the 21st Century Cures Act which was enacted in December 2016. He reviewed the criteria for RMAT designation. Benefits include interactions with FDA and possible eligibility for priority review and accelerated

approval. Eligibility for accelerated approval is based on whether the surrogate or intermediate endpoints are likely to predict long-term clinical benefit.

Dr. Bryan presented data on the status of RMAT requests that have been granted, are pending, or were denied. As of November 20, 2019, 125 requests have been received of which 36% were granted, 6% pending review, and 58% denied. The indication with the largest number of requests is neurology. It was noted that the most common product types were allogeneic cell therapy products and gene therapy products, followed by autologous cell therapy products. The majority of requests were from phase 2 studies. Analysis of denied RMAT designation requests cite administrative reasons (inactive IND, no preliminary clinical evidence), CMC reasons (different product/lack of product comparability data or not qualified as a regenerative advanced medicine therapy), or insufficient preliminary clinical evidence (study design issues, inconsistent or insufficient data). Insufficient preliminary clinical evidence or study design issues were the top reasons for denial. An overview of Breakthrough Designation (BTD) vs. RMAT requested and granted was presented, noting that 32% of BTD are granted and 36% with RMAT.

Dr. Bryan discussed the workload challenges faced by the Agency in the review and implementation of RMAT. It was also noted that businesses may respond in a variety of ways following notification of RMAT designation from companies/institutions issuing press releases with no further action, to those requesting regular follow-up contact with FDA. It was reported that the FDA is working on standardizing the number of meetings for RMAT and BTD designations.

Group discussions ensued regarding reapplications and appeals following denial. There are cases where some applicants have come back with more clinical data, resulting in successful RMAT designation. Occasional appeals that do not address the reasons for denial have been received but are generally unsuccessful. The group discussed the growing interest in utilizing Real World Evidence (RWE) however it was noted that there is tremendous variation in how information from registries is interpreted and used as well as the quality of data. Dr. Bryan suggested that if an applicant is planning to use information from a registry, they should speak to Agency about how it will be applicable in their study design. The group discussed the average time from application of BLA to approval. Dr. Bryan reported there are no currently approved products that had received RMAT designation. From a general perspective with recent approvals, the timeline from IND to approval is approximately 9 years (range 8-10) with one recent approval being shorter. There are also challenges calculating the timelines as there are various ways to manipulate the data points. For example, additional data submission requests could extend the timeline such that flexibility on the part of FDA appears to contribute to a longer timeline. The clock does not stop for these like it does for devices. There was additional discussion on manufacturing changes. Sometimes these changes are such that the product is the same but in other cases, they result in a different drug. Thus, comparability data may be sufficient for RMAT or a different IND may be required.

PRESENTATION SESSION 3: Impact of Unproven Cellular Products in the Field

- ***Presentation 3: Laertis Ikonomou, PhD (ISCT)***

Dr. Ikonomou noted that his presentation has been prepared with the support of the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapy. He discussed the challenges of meeting patient expectations with the current realities in research and clinical practice. Patients with chronic or end-stage disease may seek unproven stem cell treatments motivated by therapeutic hope. There has been a worldwide proliferation of "stem cell" clinics offering unproven, untested, and potentially dangerous treatments. This issue is compounded by differences in regulatory frameworks around the globe. The spectrum of cell-based interventions include Phase I, II, III clinical trials, innovative medical care (non-approved, possibly unproven medical interventions with appropriate informed consent, to unethical and unproven cell therapies (unproven, unregulated medical procedures without proper informed consent). Dr. Ikonomou provided a table outlining the definition of unproven cellular therapies as identified in the ISCT Presidential Task Force Reference Guide. The hallmarks of businesses offering unproven interventions include misleading advertisement, misrepresentation of risks and benefits, weak or absent scientific rationale, patient targeting, and utilizing tokens of scientific legitimacy, and exaggerated claims. This is a global issue that estimates between $300 million and $2.4 billion dollars spent and an estimated 60,000 patients treated with unproven interventions every year. A 2016 study by Turner and Knoepfler had identified 570 clinics in the US offering stem cell interventions, the number of clinics is now estimated to be over 700. These clinics cover a wide range of conditions that include aging, respiratory, immune, diabetes, orthopedic/sports injuries, and neurological. An example of an unproven "stem cell" intervention included the same day collection, isolation and re-administration of adipose tissue outside of a clinical trial. Documented adverse effects of unproven interventions have included neurological and cardiovascular issues, infections, neoplasias, loss of vision, and death.

Dr. Ikonomou noted that there has been increased regulatory action from the FDA in recent years with an increase in the number of warning letters issued. There has also been an increase in media coverage on unproven "stem cell" interventions. Following the permanent injunction against the US Stem Cell Clinic, there has been reduced offering of adipose-tissue derived products however an increase in perinatal cell-based products, cell-free products (extracellular vesicles) and cell banking services. He presented the need for continued vigilance of emerging unproven cell-based interventions that exploit regulatory "gray zones", attention to rigorous research and realistic timelines for clinical translation, manufacturing rigor, consistency and quality control, harmonizing regulatory frameworks, and the need to think globally and act locally by utilizing the national network of clinicians, scientists, patient advocates, and campaigns to educate the public.

Group discussions ensued. FDA commented that they are in a challenging position to assess over 700 clinics in the US. It was also noted that there is currently no requirement to police information posted to clinicaltrials.gov. The group discussed various ideas such as a voluntary website listing companies with products that are approved by an IRB. The challenge associated with this is that IRBs are not all equal, and

FDA is not in a position to examine all IRBs. Clinics also often move or change names therefore new IRBs are formed. The group encouraged greater efforts from FDA to educate the public, such as issuing a list of diseases with no current currently approved cell therapy products. Other ideas included improving the website design of scientific/medical organizations to increase its appeal to the public, and for organizations to adopt practices to screen their members. The lack of formalized positions or statements from medical/scientific organizations was also noted. FDA was asked if there is a process to verify an IND however it was noted that this is not an effective measure due the ease of obtaining an IND.

FDA discussed that following the Enforcement Discretion Policy, the agency will be prioritizing action on the most aggressive clinics and developers that are creating harm to the public. FDA encouraged professionals to report to the Compliance department if there are concerns that other individuals or companies are operating outside of using a legitimate protocol or IND for potential unproven cell therapy interventions. Reporting helps identify outbreaks that would otherwise be missed. Increased complexity of manufacturing processes leads to increased risks for microbial contamination and may not be picked up until the product is administered. The challenges of protecting public health information and confidentiality was discussed with FDA staff reminding attendees to work with the compliance office on these issues.

Closing comments

The agency, speakers and attendees were thanked for their participation on the topics presented. Olive encouraged the FDA to let CTLM know if there are other topics that should be brought forth and thank them for the opportunity to meet with them.