Recapping the 2nd Annual Meeting of Cell & Gene Therapy Products (CGTP): Manufacturing, Quality and Regulatory Considerations

The field of cell and gene therapy has gained significant attention over the last few years with the Food and Drug Administration (FDA) approval of multiple cell therapy products for different indications (MACI, GINTUIT, and PROVENGE) as well as the first gene therapy approval for children with spinal muscular atrophy (SMA). Indeed, the number of investigational new drug (IND) and investigational device exemption (IDE) applications to the Office of Tissues and Advanced Therapies at the FDA have nearly doubled in the last three years (Figure 1). Although these therapies have vast potential to treat or cure genetic disorders, autoimmune diseases, and cancer, the scientific community and health authorities are starting to discover how novel cell and gene therapy products work, how to administer them safely, and how to best attune the manufacturing process so that it meets demand within a reasonable timeframe. Given the continued need for a global open forum to discuss manufacturing, quality and regulatory considerations that arise from developing these products, the professional scientific society CASSS held the second meeting of Cellular and Gene Therapy Products (CGTP) on June 10th-12th 2019.

![New INDs and IDEs Submitted to OTAT CY 1963-2018](image)

**Figure 1.** Slide presented by Steven Oh, Deputy Director at OTAT/CBER/FDA. CGTP 2019 Conference.

To kick off the conference, Celia Witten, Deputy Director at the Office of the Center Director/CBER/FDA, provided some FDA perspective on the development of cell and gene therapy products. First, she showed information on how the INDs submitted for CGTP went up by approximately 50% between 2017 and 2018. She then showed a figure on 34 Regenerative Medicine Advanced Therapy (RMAT) designations that were granted, through May 1, 2019. Some rejections occurred due to product not meeting the RMAT designation, which is why it’s imperative to understand the RMAT eligibility and all existing regulatory approaches for making CGTP rapidly available.

Steven Oh, Deputy Director at OTAT/CBER/FDA, followed Celia’s talk and discussed expedited development programs – Accelerated approval, Priority Review, Fast Track (FT), Breakthrough Therapy (BT), and RMAT – in detail as well as the regulatory chemistry, manufacturing, and control (CMC) considerations behind them. For instance, he mentioned how clinical programs tend to move at a fast rate for BT and RMAT products while the early-to-late development stages are condensed. However, a rapid clinical development does not change the CMC requirements. Therefore, there should be a high
focus on all CMC and current good manufacturing practices (CGMPs) issues as early as possible if products receive BT or RMAT designation. Aligning clinical development with CMC requirements would help ensure the availability of a quality product that can be steadily made at the time of approval. Although the type and extent of manufacturing information expected at time of submission is evaluated on a case-by-case basis, the FDA representatives did point out that there are some areas of potential flexibility such as validation strategies, manufacturing scale-up/scale-out strategies, and use of post-marketing commitments or requirements.

Day 1 concluded with thorough discussions on different analytical development challenges and tools that can be used to characterize the critical quality attributes (CQAs) of cell and gene therapy products. For example, AAV quantitation assay is critical for measuring key product attributes and this may be achieved by qPCR, ddPCR, chromatography-based experiments, and other assays. One consideration examined during the panel discussions included concurrent CMC improvements (process development, analytical development, and manufacturing) to help meet timelines and avoid delays in product life cycle timeline.

Two interesting topics were introduced during Day 2 of the conference: individualized neoantigen-specific cancer vaccines and variance component analysis for autologous therapy process development. Neoantigens are novel antigens generated by tumor-specific mutations that have never been recognized by the immune system. These neoantigens are more advantageous than human antigens because they are unique to an individual tumor, they’re resistant to immune-selection, and there’s a lower risk of self-tolerance and autoimmunity. The real question is, how are they manufactured?

Syed Husain from FDA/CBER, Joel Greshock from Neon Therapeutics, and Richard Bourgon from Genentech discussed ways to design and manufacture a personalized neoantigen product. The idea is that a mutated protein will be cleaved and loaded onto a major histocompatibility complex (MHC) so that the T-cell receptor can recognize the antigen and make antibodies against it. Identifying a good quality personal neoantigen becomes key for having a therapeutic effect, but empirical identification is not feasible. Therefore, the manufacturing steps (Figure 2) become important because individual peptides must be constructed so that they match the patient’s cancer mutations.

![Figure 2. Manufacturing steps for personalized neoantigen vaccine. These steps were adapted from a presentation by Syed Husain, Senior Staff Scientist at OTAT/CBER/FDA. CGTP 2019 Conference. HLA = human leukocyte antigen.](image-url)
The variance components analysis topic was presented by Roland Ashton, Sr. Associate Quantitative Scientist/Statistician at Juno Therapeutics. Variance component analysis (VCA) is a tool that allows you to quantify sources of variability in data. For example, you can use VCA to analyze donor-to-donor variability and processing-related variability when working with autologous cell therapy. This analysis provides valuable information for creating statistically justified process designs in the future.

Comparability was the main area of focus during Day 3 of the conference. Comparability studies for proteins and biologics are essential in demonstrating that a manufacturing process change will not have an adverse impact on the quality, safety, or efficacy of a biologic or biopharmaceutical product. Due to the limited starting material, narrow structure-function understanding, and restricted analytical toolbox available for cell and gene therapy products, comparability studies can be challenging. However, a risk-based approach and maintaining close communication with health authorities throughout product development can help overcome comparability challenges.

This year, Heidi Zhang joined Bruce Thompson and Andrew Weiskopf in co-chairing the 3-day symposium at the Hyatt Regency Bethesda Hotel in Bethesda, MD. There were a total of 245 attendees (172 of them first-time attendees), representatives from 15 countries and 87 companies, 18 regulators, and 30 speakers. The CASSS Mobile App allowed attendees to access schedule, presentation slides, speaker abstracts, and network with fellow attendees.

Remember to mark your calendar for next year’s CGTP conference again in Bethesda from June 8-10, 2020.