Synopsis of the CASSS meeting on of Cell & Gene Therapy Products: Manufacturing, Quality and Regulatory Considerations

The three day meeting (10th-12th June 2019) was organized by CASSS and a number of speakers presented on the current research, developments and challenges in the field of cell and gene therapy. The meeting started with presentations given by representatives from the FDA on the current regulatory status of advanced therapy medicinal products (ATMPs), products specifications to be considered as ATMPs and on the future guidelines the FDA is working on. Dr. Celia Witten introduced the audience to collaborations of FDA with Nexight and National Institute of Standards and Technology, which are focused on developing new standards for regenerative medicines. The activity of the FDA in the gene therapy field is mainly focused on developing manufacturing standards, harmonization technical guidelines via the IPRP program (www.iprp.global/home), promotion of existing guidelines via APEC committee, and encouraging sponsors to early interactions with FDA (INTERACT program). Furthermore, Dr. Steven Oh from the FDA discussed the undergoing work on bringing the medicinal products quicker to the patients while ensuring product’s safety. Several expedited programs for granting products approval are present (Accelerated approval, Priority review, breakthrough therapy (BTD), Regenerative Medicine Advanced Therapy Designation (RMAT)). Approvals via RMAT program are higher now compared to BTD, showing an increasing trend towards medicine with substantial genetic modifications addressing unmet medical needs for serious diseases or conditions. Dr. Oh also talked about the common reasons medicines were not granted approval, of which most common was the lack of CMC and cGMP data on the product itself as well as raw materials.

The topic which gained most attention throughout the meeting was on the challenges present in chemistry, manufacturing, and controls (CMC) activities. Dr. Alexandra Beumer started the topic with her talk on breaking the traditional CMC development pathway. She discussed the lack of guidelines for CMC data frameworks where each submission has to be treated on case-by-case basis, as well as the lack of experience the industry has in this field. The presented challenges were mainly: limited analytical toolbox, limited amount of samples and batches to perform stability and comparability studies, and lack of a clear validation processes. The proposed strategies to mitigate the challenges were to consider development of robust assays early in development process to avoid major changes in analytical methods later on, saving material from early stage development and considering ex vivo potency assays. Dr. Tam Soden presented the current status and encountered challenges in characterization of CAR-T cells (1 product approved, within next 10 years 15 more products are expected). Main concern is the lack of known critical quality attributes (CQAs) for cell therapy products. Currently, most CQAs tests and validations are performed on
a risk-based approach build on the impact of an attribute towards product’s efficacy or patient’s safety. Kite Pharma developed an internal risk assessment with a scoring system from 1 to 45 based on combination of severity and uncertainty of risk. Examples of CD8+ and CD4+ T cells, and poly-functional cytokine production were given as case study examples where CQAs are difficult to determine and validate. Furthermore, Ilya Shestopalov described the lessons learned from their recently approved Zyntelgo - combination cell and gene therapy product for transfusion-dependent β-thalassaemia. Several types of methods for measuring drug potency were tested, where vector copy number and transduction efficiency showed the lowest precision in determination of potency, whereas the rescue of disease associated biomarker and therapeutic protein expression methods showed highest validity. Dr. Julia Deuel and Dr. Carl Co discussed the current analytical techniques for characterization of viral vectors and in the past years, little progress has been made in this area. Current most commonly used techniques are SV-AUC, IEX-HPLC, SEC-HPLC, UV spectroscopy, CD-MS and FFF-MALS. However, each technique has its limitations and disadvantages. During the panel discussion, many participants raised their concerns on the TCID50 assay with respect to its repeatability (100-200% variation) and usefulness in characterization of ATMPs. On the second day, continuation of talks on CMC challenges and regulatory aspects were continued as well as presentations on ATMPs manufacturing were delivered and neo-antigen therapies were delivered. Organization and planning of infrastructure for production of ATMPs is much more complex and time consuming than for standard protein based drugs, although the technology and production lines are similar. Dr Alexandre Juillert was discussing the TALEN method for gene editing in CAR-T cells developed by Cellectis. The method presented high precision (targeting within 6 base pairs of any target in genome), specificity (recognition site is 32 base pairs long) and efficiency (>95% for TCR-alpha). Individualized neo-antigen specific therapies were presented by Dr. Richard Bourgon as alternative path to vaccinations for priming T-cell responses. However, the products is still early in development and research is undergoing to bring it to the market.