INSIGHTS FROM THE BDO LIFE SCIENCES PRACTICE

CMC HURDLES REMAIN DESPITE RECENT CELL AND GENE THERAPY PRODUCTS SUCCESSES

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Recent therapeutic advances derived from innovative cell and gene therapies (C&GT) have left companies' manufacturing and product characterization efforts gasping to keep up. The design and creation of altered cells, by intervention directly in their genome for use against cancer and other defective gene targets, has been stunningly successful. These successes have been driven to the market so quickly that creating the know-how to analyze and consistently manufacture these products has lagged. Consequently, CMC development activities can't keep pace with the dramatic successes in the clinic since little technical understanding is available during early development. However, this is rapidly changing.

REGULATORY COLLABORATION DRIVING HIGHER LEVELS OF INDS

While C&GT product development must still conform to traditional regulatory milestones for commercialization, the amazing progress for new cell and gene therapies is due in large part to a heightened level of collaboration between companies and global regulatory agencies. This collaboration has contributed to twice the number of new C&GT INDs in the last two years compared to the previous ten years. In addition, programs such as FDA's INTERACT, IPRP and reflection papers from the EMA are helping companies promote early and informal problem solving.

NAVIGATING THE SIMULTANEOUS CHALLENGES OF CONSISTENCY, ANALYTICS AND PRODUCTION

The take-home message is that design and development of new C&GT therapies at small scale is not the problem. The difficulty is demonstrating consistent lot production histories, while scaling-up with new analytical methods and changing sites of production. Complicating this picture is the difficulty in distinguishing between cell differences due to manufacturing variabilities vs. patient populations. This issue is causing companies to use statistical methods to understand donor cell variability to inform manufacturing decisions. Consequently, analytical comparability studies now occur much earlier in development with fewer patient numbers.

These gaps in CMC knowledge make it hard to know what constitutes a complete and successful regulatory package. And obligatory post-approval commitments contribute additional urgency to the speed of development activities and strict management of timelines. The rapid pace of progress forces companies to prioritize and plan all CMC activities and to engage regulatory outreach programs early in development.

This approach, coupled with an industry that is learning from itself, has propelled companies to overcome accelerated development constraints.

A PATH FORWARD LEVERAGING NEW TECHNOLOGIES

Case studies at the June 2019 CASSS Cell and Gene Therapy Products Meeting focused on successful technologies in three main product development areas. These were: engineered patient cell therapies; *in vivo* gene editing directly in somatic cells; and personalized vaccines from unique mixtures of tumor cell surface fragments (neoantigens). Several presentations detailed how companies have handled the complex and changing production decisions and analytical comparability strategies while developing the technologies to do so. Also, late stage process characterization and validation activities along with new product ideas were openly discussed. Representatives from six worldwide regulatory agencies (FDA, Health Canada, MHRA-UK, MEF-Netherlands, Taiwan FDA and Infarmed-Portugal) participated and several discussed their experiences and expectations for the benefit of companies.

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