Managing Accelerated Development Industry Experience

CASSS 2019 Cell & Gene Therapy Products Symposium

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CAR T cell therapy

- Transformative potential
  - Rapid clinical development to help patients in need
  - Field in early stages
Region-specific regulations for genetically modified cells

Additional measures to ensure environmental and patient safety prior to clinical trial initiation

- **US**
  - Up until August 2018, NIH had reporting requirements under Appendix M of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
  - Apr 2019: Removal of these reporting requirements with NIH finalized
- **EU**
  - GMO applications required per country
- **Japan**
  - Strategic Consultations required prior to a Clinical Trial Notification for Regenerative Medicine products
  - Confirm product is not subject to the Cartagena Act in Japan

Understanding region-specific needs is critical for enabling global development
Autologous CAR T cell manufacturing

**Leukapheresis**
- Apheresis material obtained from patient via standard leukapheresis collection

**PBMC Isolation**
- PBMCs isolated

**Cell Activation, and Transduction**
- Culture initiated, T cells activated, and transduced with vector to insert CAR sequence

**Cell Expansion, Harvest, Cryopreservation**
- CAR T cells expanded to therapeutic dose, formulated and cryopreserved.
- QC/QA release

**Infusion**
- CAR T cells infused into patient after lymphodepleting chemotherapy
Development challenges

- Variability in starting cell composition
  - Wide process variability

- Limited starting cell material
  - May require different approaches for process characterization and product characterization
  - Begin commercial planning while still in learning phase

- Vector manufacturing and cell processing require optimization in order to enable consistent commercial supply of the CAR T product

- Setting drug product specifications can be difficult since mechanism of action is not straightforward

- Limited platform and/or industry knowledge

Significant CMC changes may be required prior to, during, and after pivotal trial
Keys to success

- Prioritization of CMC changes and implementation prior to pivotal trial
  - Addition of manufacturing sites?
  - Fresh or frozen starting cells?
  - Raw materials of biological origin to be replaced and/or dual sourced?
  - New analytical methods?

- Retain sufficient samples

- Proactive discussions with Agencies as needed
  - BTD and RMAT designation allow for timely interactions with the FDA
  - PRIME designated products have an early CHMP Rapporteur appointment and an EMA quality specialist
  - During clinical development of regenerative medicine products, CMC information is mainly communicated through preliminary meetings and consultations with the PMDA, which is different from other product categories in Japan
Case study: site addition for an ATMP

- **Change:** Manufacturing site addition for an autologous CAR T
  - Vector or drug product for the pivotal trial manufactured at site A
  - Commercial vector or drug product to be manufactured at site B

- **Context**
  - Rapid development often requires manufacturing to start in site A
  - Understanding of the manufacturing process is evolving

- **Considerations**
  - Demonstration of analytical comparability is key
  - Clinical manufacturing experience at site B prior to commercial manufacturing is desirable

- **Approaches**
  - Separate formal Agency meetings
  - Frequent interactions with an Agency
Typical interaction during development: formal meetings

- Plan is ready. Submit meeting request to FDA
- Submit meeting package (wk 4)
- Revise plan (wk 10)
- Initiate study (wk 11)
- Submit IND (wk 25)
- EU approvals (wk 33 - 37)
- Submit IMPD (wk 25)
- EU Letter of Intent
- Scientific Advice Day 40 (wk 31)
- Scientific Advice Day 70 (wk 35)

Time from initial plan to release of initial lot: 31 weeks
Possibility of different recommendations from different Agencies
Proactive, frequent interactions with Health Authorities

Plan is ready.
Email plan to FDA

Informal TC (wk 2)
Email revised plan (wk 4)
Submit IND – revised plan
Receive ok via email
Initiate study (wk 5)

Submit IND – results (wk 19)

Release initial lot (wk 25)

Week 5 10 15 20 25 30 35 40 45

Time from initial plan to release of initial lot: 25 weeks
Less risk due to confirmation of revised plan prior to execution
Input from one Agency only

* Scenario is also applicable for EU member states, Canada
Summary

- Regulatory tools to enable fast-to-market cell and gene therapy products
  - BTD, RMAT, PRIME designations help enable rapid development
  - Mechanism to confirm the best approach for asking questions is also helpful

- Additional efforts which could help expedite development
  - Standardization of analytical methods
  - Certification scheme for critical raw materials in the EU
  - Consultative advice