Search Less, Know More

The essential tool for regulatory, compliance, & quality professionals

CMC Considerations for Cell and Gene Therapy Products

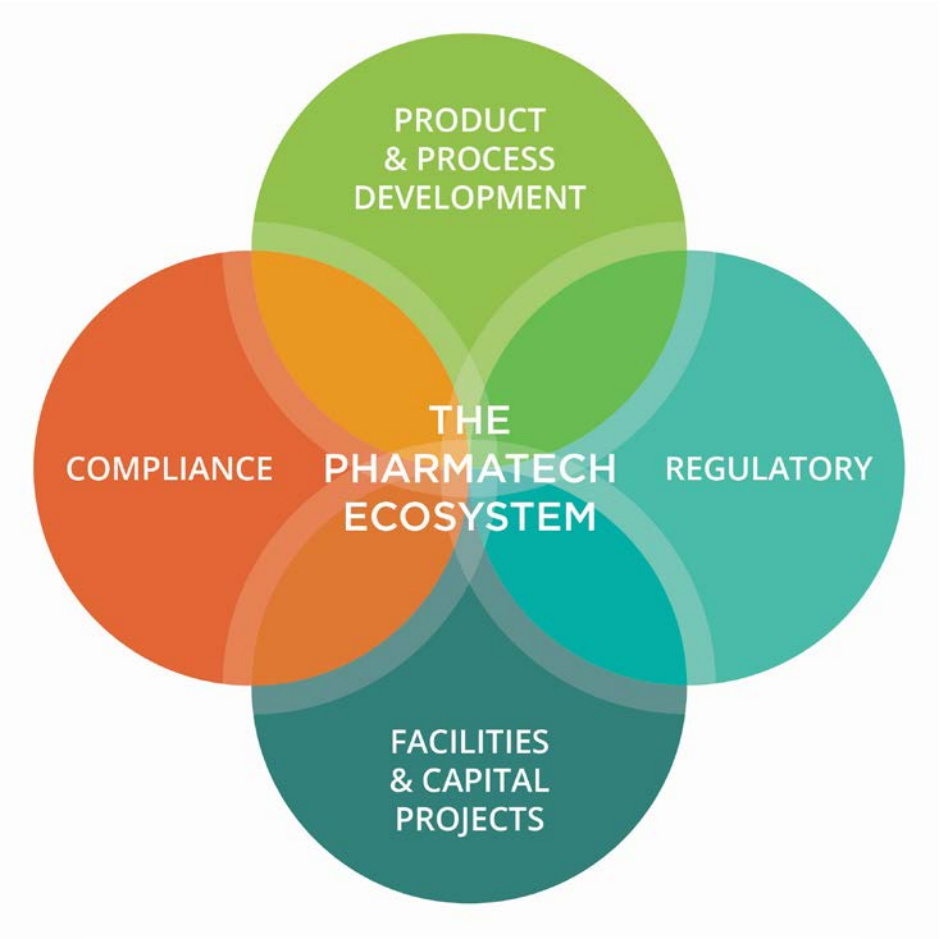
Presented by:

Adam Lambert
VP of Product and Process Development at Pharmatech Associates

www.govzilla.com
help@govzilla.com
(844) 332-3320

pharmatech™ associates

The Pharmatech Ecosystem



Our Subject Matter Experts have fully integrated development knowledge across all core elements of the drug development lifecycle. For our customers this means better, more informed, decision making; smaller, nimbler teams and the ability to support multiple impacted areas within the development lifecycle more efficiently.

Introduction and Overview

Concept of Cell and Gene therapy has been around for a relatively short time

- First Transplant of Hemopoietic Stem Cells in 1957 - Bone Marrow Transplant for the treatment of Leukemia

- Currently the FDA has approved 18 Cell and Gene therapy products.
  - https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
- Clinicaltrials.gov has over 37,000 trials listed for cell therapy
- Over 1000 CAR-T cell trials, with 40 in Phase 3 (approx. 400 patients and 4-6 year trials)

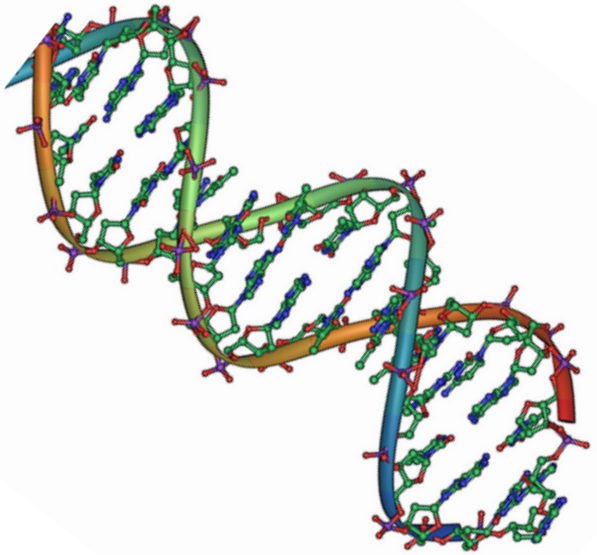
pharmatech associates

Introduction and Overview

- Development Overview
  - Production Processes
  - Supply Chain
  - Analytical Methods
  - Reference Standards
  - Specifications
  - Ancillary Materials
- Case Studies
  - CAR-T Cell Therapy
  - Luxturna - Spark Therapeutics

Cell and Gene Therapy Production Processes

- Upstream Processes
  - DNA Production
  - mRNA Production
  - Viral Vector Production (Gene Packaging)
  - Cell collection, production and expansion
- Downstream Processes
  - Viral Vector Production (Gene Packaging)
  - Product Formulation
- Post-Production
  - CCIT
  - Cold Chain Storage and Distribution

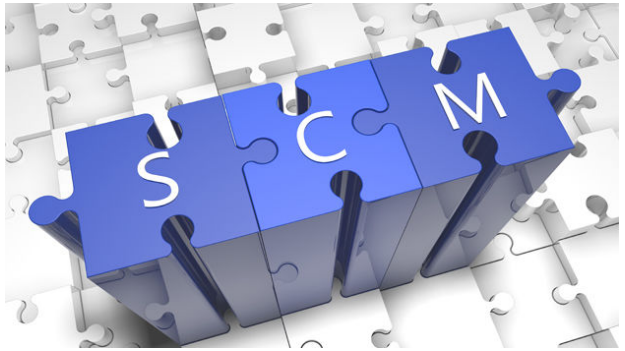


Complexity of the Supply Chain

- Raw Materials
  - Complex materials (some products you have a person as part of the supply chain)
  - Availability - Few suppliers, non-GMP
- Multiple Vendors producing Critical Components
  - Data Management
  - Quality By Design considerations
  - Specifications (Raw/Ancillary Material, In-process, finished product)
  - Tech Transfer (Methods between Vendors)
  - Communication of information
- Shipping
  - Maintaining Cold Chain (-80 C in many cases)
  - Shipping Validation (Shake, Rattle, Roll for RM, DP and DS)

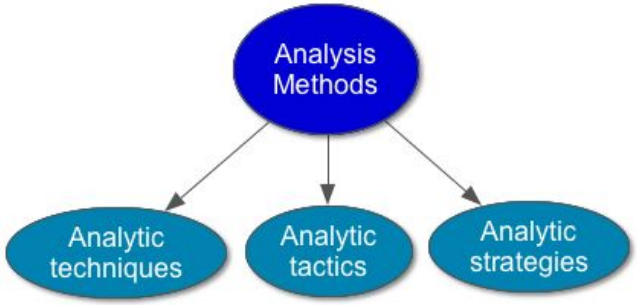
Supply Chain Management

- Software tools for management of Data and processes
  - QBD Software
  - Data Management Software
- Vendor Selection and Qualification
- Communication with Vendors
  - Between the sponsor and vendor and between vendors
- Agreements that allow transfer of critical information between vendors
  - Critical Quality Attributes, Scheduling, Methods



Analytical Methods

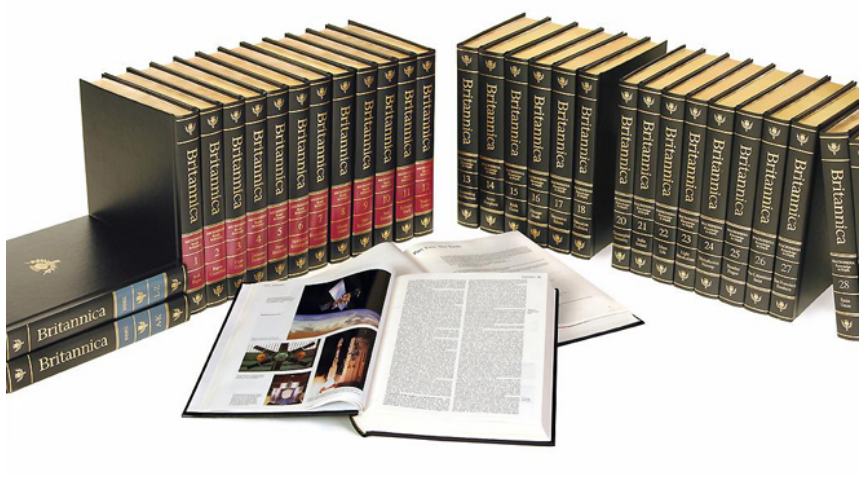
- Significant amount of testing is required
- Testing includes CPP and CQAs, ancillary materials
- CPPs are a significant portion of tests performed due to the complexity of production processes
- Multiple potency methods may be required in order to ensure product consistency due to inherent variability in methodologies used.



* There is some debate as to the current ICH definition of CPPs and CQAs appropriateness for Cell and gene therapy products. A broader definition may be appropriate as there may be some unknown CQAs that impact safety and efficacy

pharmatech associates

Reference Standards



- Reference Standard Identification
  - Needed for CPP, CQA and Ancillary Material testing
- Reference Standard Sourcing
  - Many novel tests, and reference standards are not readily available
- Reference Standard Qualification
  - Novel reference standards need to be appropriately qualified

DS and DP Specifications

- The Quality Target Product Profile
- Determination of Critical Quality Attributes
  - Critical Quality Attributes may change during development
- When setting product specifications it is imperative that the justifications be adequately challenged internally
- Excipient concentrations should be considered
- Adventitious agents and contaminants

pharmatech associates

Ancillary/Raw Materials

- USP <1043> covers the use of ancillary materials in cellular and gene therapies detailing the risk assessment and qualification requirements
- Gene and cell therapy products differ significantly from traditional biotech products in that many ancillary materials used are equivalent to excipients (given along with the therapeutic to patients -ie. Cryopreservation Medium)
- It is recognized that a significant number of ancillary materials are not produced under GMP
  - Assurance of quality, consistency, availability
- Risk Assessment

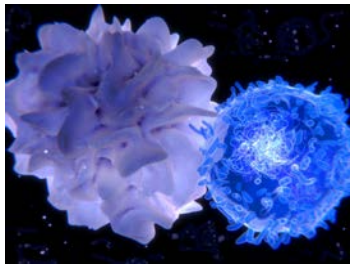
USP <1043> Qualification Requirements – Risk Based

- Identification
- Selection and Suitability for Use
  - Selection process should be documented
- Characterization
  - Critical quality attributes including functionality
- Vendor Qualification
  - Production Processes, Testing Procedures, Audit History, Certifications
- QC and QA
  - Testing and traceability of materials

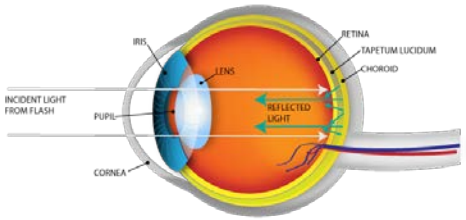
pharmatech associates

Case Studies

- Overview of Complete Response Letters for Cell and Gene Therapy Products
- Two Case Studies will be Presented
  - CAR T-Cell Therapy
    - Cell Therapeutic/Personalized Medicine
    - Complex manufacturing supply chain/process



- Luxterna - Gene Therapy using AAV for Gene delivery
  - Gene Therapy Product/Specific but not Individualized
  - Orphan Drug Approved as first in class product

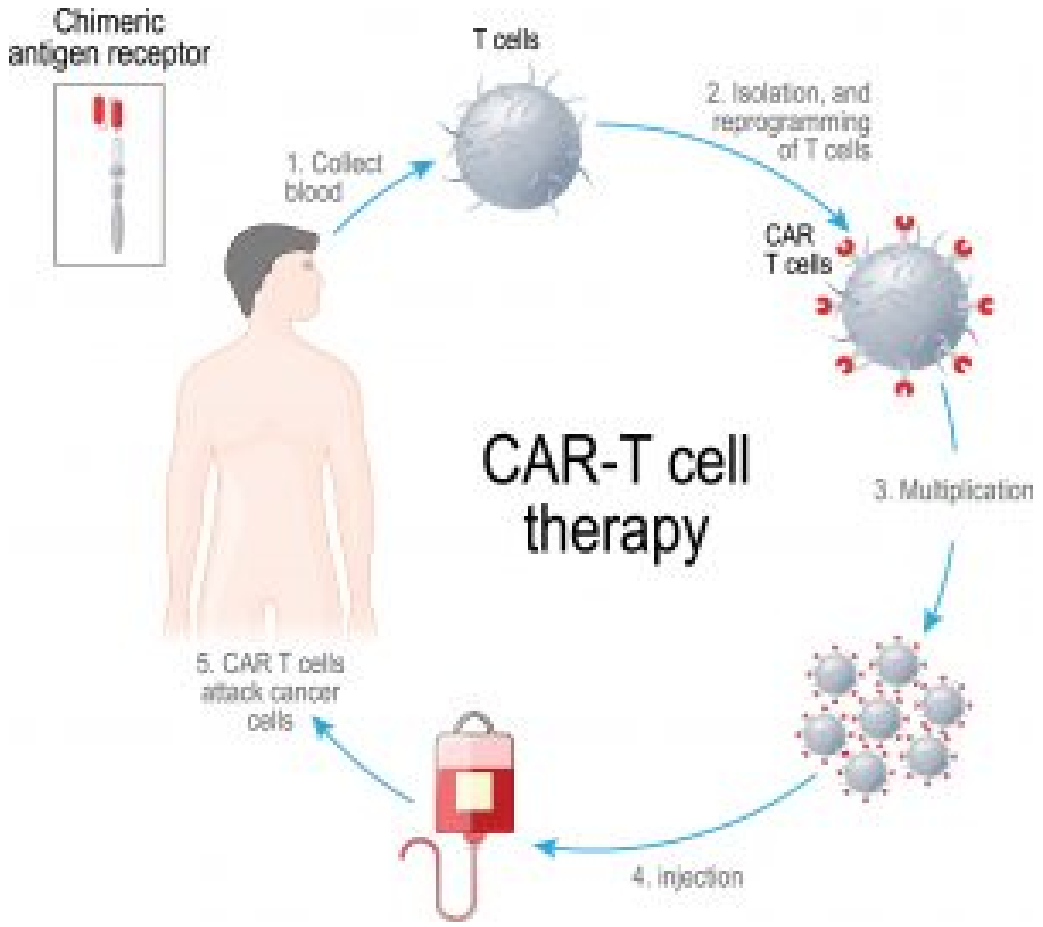


Complete Response Letters (CRLs) for Cell and Gene Therapy Products

- Biomarin (2020) Hemophilia Gene Therapy Product
  - No CMC Issues, FDA introduced new clinical recommendation for 2-year durability follow up
- Ezyvant (2019) Infant Thymus tissue transplant for T-cell disorders
  - CRL issued due to Manufacturing Concerns
- BMS/Bluebird (2020) CAR T-Cell Cancer (Multiple myeloma) Therapy
  - Refusal to File - CMC Related. Resubmitted July 29, 2020

- Companies developing products are unwilling to “air their dirty laundry”

CAR T-Cell Therapy



- Complex Process
- Multiple factors impact the efficacy of the therapeutic
- Additional genes are being identified to improve efficacy and scope of treatments
- New Reagents/materials are being developed that will improve safety, production efficiency and ultimately reduce cost

CAR T-Cell Therapy

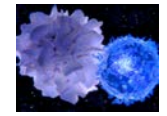
T-Cell Transport

Thaw and Infusion in Patient

Apheresis Collection

Apheresis Product Wash

T-Cell Activation

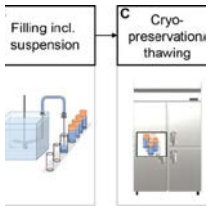


Gene Transfer

T-Cell Expansion

T-Cell wash and formulation

T-Cell cryopreservation



Separate cGMP Process

Compliance Through Science®

pharmatech associates

CAR-T Cell Production

- Multiple technologies/reagents are available to perform each step of the process. Selection of reagents will define the safety and efficacy CQAs
- Optimal Conditions for one step will influence the results of following steps
  - ie – Number of beads used for collection/wash could impact ability to perform activation if beads are not removed
- It is unlikely that a single source vendor is used for all critical steps. i.e the Viral vector production will likely be with a different vendor
- Risk assessment and control strategy needs to take into account all steps, unit operations, and source materials used
- It is OK to use-non-GMP materials if appropriate qualification of the material is performed and described
- Data management from development to GMP clinical and commercial production is critical

Real World CAR T-Cell Manufacturing Issues

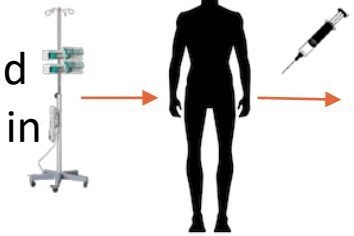
- Novartis Cell Viability- Kymriah
  - 6-7% of batches produces can not be sold due to cell viability
  - Set Specification (80%?) is not achievable routinely
    - seems like it was arbitrarily obtained, or from a limited data set
  - Lots that Fail are allowed to be administered under compassionate use
    - Free for the Patient 
    - Efficacy is observed in patients who receive lots that do not meet cell viability requirements
- What is the Cause? What is the solution?

pharmatech associates

CAR T-Cell Therapy

T-Cell Transport

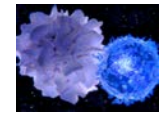
Thaw and Infusion in Patient



Apheresis Collection

Apheresis Product Wash

T-Cell Activation

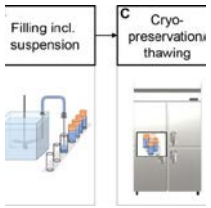


Gene Transfer

T-Cell Expansion

T-Cell wash and formulation

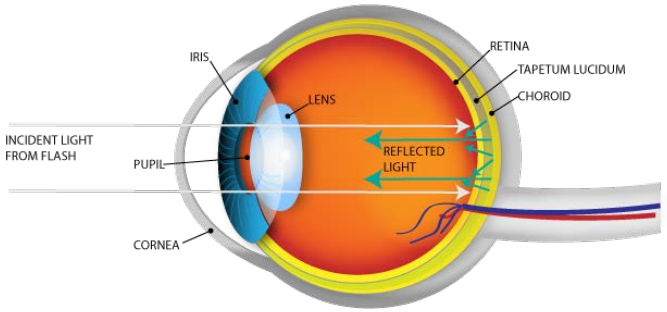
T-Cell cryopreservation



Separate cGMP Process

Compliance Through Science®

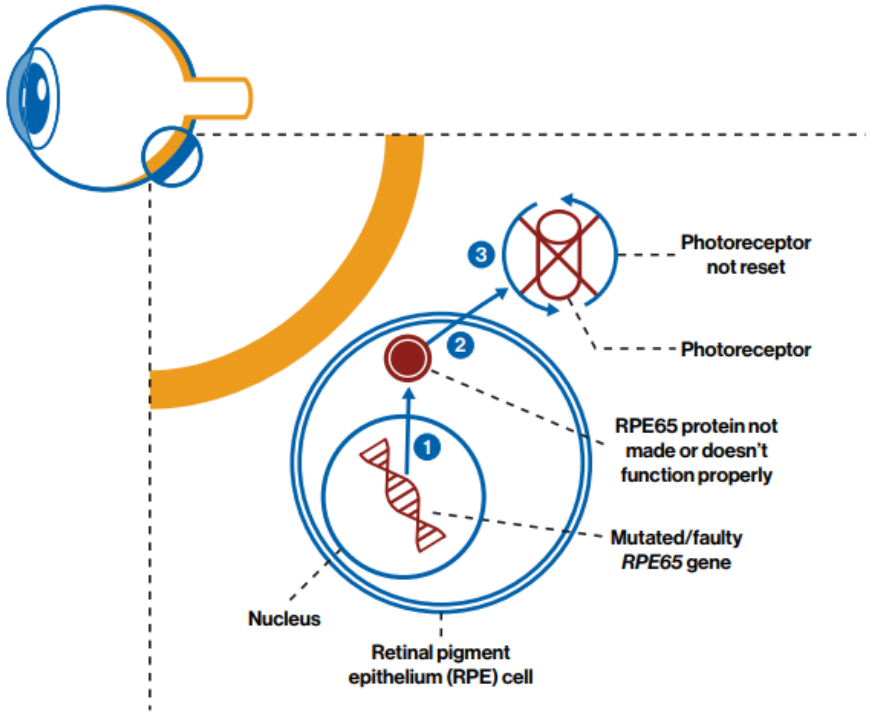
Luxturna – Spark Therapeutics (Approved Dec 2017)

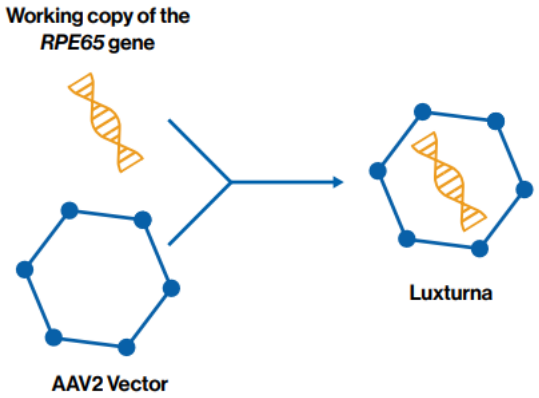


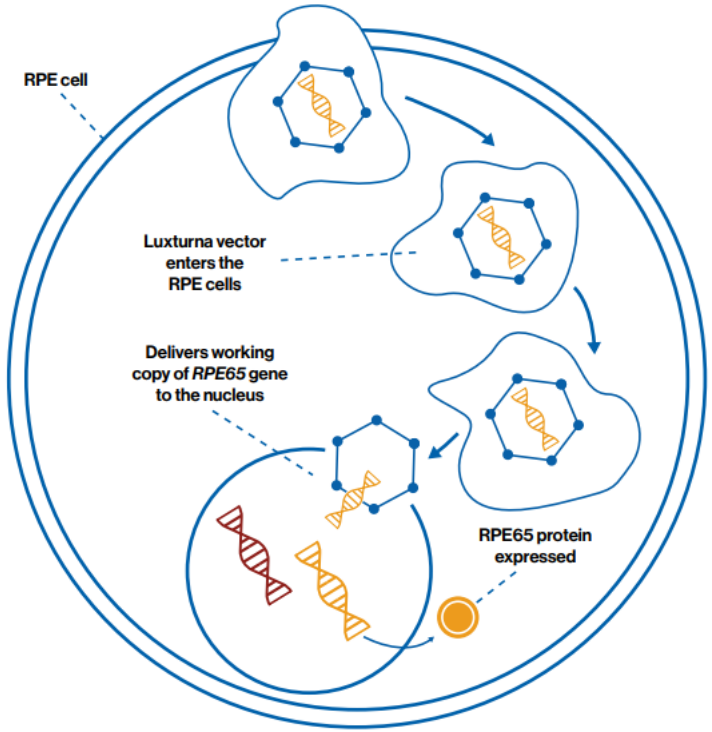
- Pharmacological Category - Adeno-associated virus vector-based gene therapy
- Indication: the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy
- Initial submission - May 16, 2017, Filed by FDA on July 14, 2017
- Approved Dec 2017

Disclaimer: I was not involved in the development of this product nor do I have any connection to the company – This is based on the review of documents available on the FDA website

Product Mechanism of Action Overview







Images are from Luxterna Promotional Materials

AAV Production Process

Optimized harvest and transfection process

Recovery and stabilization of crude virus from cell culture systems

Concentration, formulation, and filling of vectors

Master cell bank and cell expansion adherent in cell culture

Cell Expansion

Transfection with 2–4 plasmid vectors

Plasmid Transfection

Virus production phase post-transfection

Virus Production

Virus Recovery

Virus extraction, clarification, and concentration

1- or 2-step purification process ahead of DS formulation

Purification

Drug product production

0.2-µm filtration and vial filling

Cell expansion and production using adherent cell factories

Optimized harvest and transfection process

Purification on affinity-, charge-, and size-based processes

Tony Hitchcock, Vera Lukashchuk and Kevin Bowes. *Development Approaches to Adenoassociated Virus Production*, Bioprocess International September 2017

Luxturna CMC

- Product Submitted May 17, 2017
- Submission accepted July 14, 2017
- CMC Review Complete and found acceptable on Dec 9, 2017
- In this time there were
  - 16 CMC information requests outlining deficiencies/clarifications
  - 58 Amendments were made to the submission

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Identified CMC Information Requests and Deficiencies: Brief Summary

- The complete data and purpose for all produced lots was not clearly presented.
- Complete annotated sequences for all vectors used in the production was not provided
- SOPs for qualification of starting materials was not provided
- A complete list of all materials used was not presented
- Plasmid purification processes and associated cleaning verifications were not provided
- Data supporting the DS and DP specifications was not clearly presented. Justification of specifications was not sufficient

Identified CMC Information Requests and Deficiencies (Cont.)

- An Assay for subvisible particulates was not provided
- Comparison of results from different manufacturing sites was not presented clearly. Statistical comparison of results between sites was not presented
- Shipping validation reports for the DS and DP were not provided
- Updates to Stability Data were requested (only 3-9 month data was presented, ultimately 18 month shelf life was approved)
- Diluent Development Studies were incomplete
- Storage and distribution information of DP post secondary packaging was not provided, storage temperatures proposed were not justified
- Data for methods supporting suitability for use was not provided
- Proposed specifications were too wide and not supported

Identified CMC Information Requests and Deficiencies (Cont.)

- Testing of pooled harvest samples is not acceptable (Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (2010)
- Working standard qualifications
- Clinical data do not support broad acceptance criteria
- Please Update the BLA with the Changes by Tomorrow

https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

pharmatech associates

Post Marketing Commitments

- Employ a statistical sampling plan (AQL) and appropriate acceptance criteria for critical and major defects of the DP
- Perform Cleaning verification as PMC

pharmatech associates

Overall Message

- Processes are complex and with technology and treatment advances, ease of development will improve, while the complexity of the processes expand
- Data Management plan should be established early and be comprehensive
- Properly set Specifications for the product and provide appropriate justification. This includes all Ancillary materials and process intermediates. Specifications may change, which makes setting and monitoring the specification evolution critical
- Establish a comprehensive CPV plan (process validation and control strategy)

pharmatech associates

Questions?

Contact Information

Adam Lambert Ph.D., Vice President, Product and Process Development
alambert@pai-qbd.com
Bikash Chatterjee, Chairman and CEO
bchatterjee@pai-qbd.com
Pete Rafa, Executive Director, Project Design and Start-Up
prafa@pai-qbd.com
Pharmatech Associates, Inc.
22320 Foothill Blvd. #330
Hayward, California 94541
Toll Free: 877-787-0177

Visit our website a
www.pharmatechassociat n
Follow us
https://www.linkedin.com/company/pharmatech-associates/

Compliance Through Science®