Regulation of Manufacturing Cell & Gene Therapy Products For Use in Phase I Clinical Trials

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Thank you for the Invitation

I have no disclosures to make
Center for Cell & Gene Therapy

- Partnership between Baylor, Houston Methodist & Texas Children’s
- ~400 staff
- ~50+ INDs on Cell & Gene Therapy
- 2 cGMP facilities (cells & viral vectors) with 22 clean rooms
- Manufacture products for Phase 1 & 2 clinical trials
Aim

• To review the regulatory process for cellular products to be used in Phase 1 clinical trials

• To describe the CMC process for Cell Therapy products

• Intended for those in early stage development
Many cell and gene therapies originated in basic research laboratories.

Few investigators were aware of requirements for manufacturing a therapeutic product.

Few were aware of regulatory requirements to initiate a clinical trial.

As a result the transition from bench to beside was often prolonged.
In parallel the FDA was evolving a regulatory strategy to deal with this rapidly-evolving area of medicine.

A risk-based approach was developed with its foundations in the pharmaceutical regulations.

Most cell therapy products fall into the high risk category.

This requires cGMP manufacturing of the product and conduct of clinical studies under an Investigational New Drug approval.
Consequences

- Academic centers had to learn cGMP regulations
- Many built clean room manufacturing facilities
- Manufacturing staff had to be recruited and trained
- A Quality infrastructure had to be developed
- Funding sources needed to be found
Resulting Issues

- Some confusion as to what defined a product as “high risk”
- Understanding of cGMP varied widely
- Not clear what degree of compliance was required
- Cellular products raised issues not encountered with small molecule drugs
Addressing the Issues

High Risk

- More-than-Minimal manipulation ex vivo
  - Expansion
  - Genetic modification
  - Activation

- Non-homologous use
FDA Guidances

- Guidance for Industry
  - Guidance for Human Somatic Cell Therapy and Gene Therapy
  - Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products
  - Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products

Dates:
- Cell & Gene Therapy 1998
- Minimal Manipulation 2014
- Homologous Use 2015
GMP Compliance for Phase I
2008

- Staff
- Quality Plan
- Facility & Equipment
- Component/Closure Control
- Manufacturing & Records
- Lab Controls
- Packaging
- Recordkeeping
Cell Therapy: Concerns

- Lack of clinical experience
- Different methods for delivery
- Differentiation/Migration
- Uncontrolled gene expression
Differences between cells & small molecule drugs

- Persistence of product
- Immunogenicity
- Differentiation
- Migration
- Dose limitations based on manufacturing
- Duration of manufacturing
Cell Therapy: CMC Issues

- Biological with natural variability and complexity
- Potential for adventitious agent contamination
- Use of aseptic manufacturing
- Stability for distribution
- Need for rapid release testing for fresh cells
CMC: Information Required

• Product Manufacturing
  – Components & Materials
  – Procedures

• Product Testing
  – Microbiological testing
  – Identity
  – Purity
  – Potency
  – Other
CMC: Information Required

• Final Product Release Criteria Testing

• Other issues

  – Product Tracking
  – Labeling
  – Container/Closure
  – Environmental Impact
  – Qualification of Manufacturing Process
  – Biostatistics
Cells

- Autologous/Allogeneic
- Sources (blood, fat)
- Mobilization protocol
- Collection/Recovery method
- Donor screening & testing (not for Auto)
Product Manufacturing
Components and Materials

• Cell Banking System
  – History, source, derivation, characterization
  – Master Cell Bank
    • Sterility
    • Freedom from viruses
    • Cell identity
    • Purity
    • Functionality
    • Manufacturing & storage
    • Genetic/Phenotypic stability
  – Working Cell Bank
    • Sterility, In vitro virus, Mycoplasma, Limited identity testing
Product Manufacturing
Components and Materials

Reagents used for Manufacturing

- Affect safety, potency, purity of final products
- Tabulate
  - Concentration at manufacturing step
  - Vendor/supplier
  - Source: human, bovine etc., country of origin, testing etc.
  - Quality: C of A for reagents
- Qualification if not FDA-approved
- Removal from final product: patient sensitivity
Product Manufacturing
Excipients

Component of final product e.g. DMSO

• Concentration in final product
• Source
• Qualification
Product Manufacturing Procedures

List/Summary of all procedures used in

- **Collection**: volume, #, separation, open vs. closed collection
- **Irradiation**: demonstrate efficacy
- **Final harvest**: fresh vs. frozen, storage

Manufacturing time

- During production and storage

Final formulation

- Excipients
- Cell concentration
- Shipping if cryopreserved
Product Testing

Microbiological

• Sterility: 21 CFR 610.12, Rapid Methods

• Removal of antibiotics: Bacteriostasis/Fungistasis assay

• In-process and final product

• Fresh products: 48 & 72 hours pre + Gram stain + 14 day follow-up testing - with action plan if results positive
Product Testing

Mycoplasma

• Approved testing method (USP)

• Rapid Methods for fresh products
  – PCR, MycoAlert

• Check with FDA for validation requirements
Product Testing

Identity

• Identify product

• Distinguish it from others in the facility
  – Cell surface markers
  – Genetic polymorphisms
Product Testing

Purity

• Residual contaminants
  – Antibiotics
  – Proteins
  – Cytokines etc.

• Endotoxin
  – LAL
  – <5EU/kg/hour
Product Testing

Potency

- Describe & justify assays used
- Quantitative better than qualitative
- Must measure appropriate biological activity by start of Phase 3

Other

- No general safety testing
- Viability $\geq 70$
- Dose
Release Testing

• Based on assays just described
• Results available before administration?
• Provide as Table
• Include test sensitivity & specificity
• Describe actions taken if positive sterility reported after infusion
Product Stability

- In storage stability: pre-freeze to post-thaw
- Effects of cryopreservation
- Stability between thawing & administration
Other

• Tracking
• Labeling
  • Specific language
• Containers
  • Compatible with product
Qualification of Manufacturing

- Method for appropriate oversight
- Consistency in manufacturing & quality
- Products safe, pure & potent
- Effective quality system in place
The Key to Success!

Step-by-step guidance to writing the CMC section

Template provided

http://www.fda.gov/OHRMS/DOCKETS/98fr/03d0349gdl.pdf
Advice

• Read and follow the Guidances

• Use Pre-pre and Pre-IND Meetings with CBER Office of Cellular, Tissue and Gene Therapies
Product Manufacturing

Components and Materials

- Document source of all materials and components
- Summarize testing performed
- Provide CofA from manufacturer