


Cell Therapeutics - Process Development and Manufacturing for Human Clinical Trials

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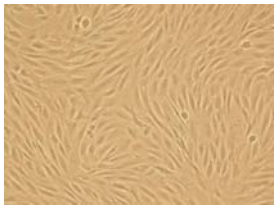
Challenges in the Development of Cell Therapeutics



- cGMP compliance issues -
  - GMP compliance progression – Phase 1 to commercial
  - Donor eligibility requirements – 21 CFR 1271
  - Development of manufacturing/QC documentations
  - Validation of manufacturing process including aseptic processing
- Manufacturing process challenges –
  - Variability in starting material – donor/cell line variability
  - Variability in raw materials – FBS, media components, attachment matrices
  - Scalability of the manufacturing process – research scale to commercial
- Quality Control challenges -
  - Appropriate potency assay may be challenging to identify
  - **Cell therapeutics are extremely complex - the product is the process**

Development Project Stages

Project management – team effort in collaboration with program PI

- Technology transfer in
- Process and assay review
- Process and assay development
- Process and assay qualification
- Clinical production and QC testing
- Technology transfer out

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Development of the Manufacturing Process

- Technology transfer in – research process/publications
- Review of manufacturing process
  - Process scalability –phase 1 to commercial
  - Process validation - future FDA requirements

- Review of raw materials
  - Cell seed banks or donor tissues
  - Critical and high risk RMs - animal-derived, undefined, variable quality
  - Quality issues – vendor qualification, QC testing, traceability
- Process qualification and validation
  - Aseptic processing
  - Qualification trials
  - Process validation – Phase 3

- Process deficiencies not addressed early can become more expensive problems later in development

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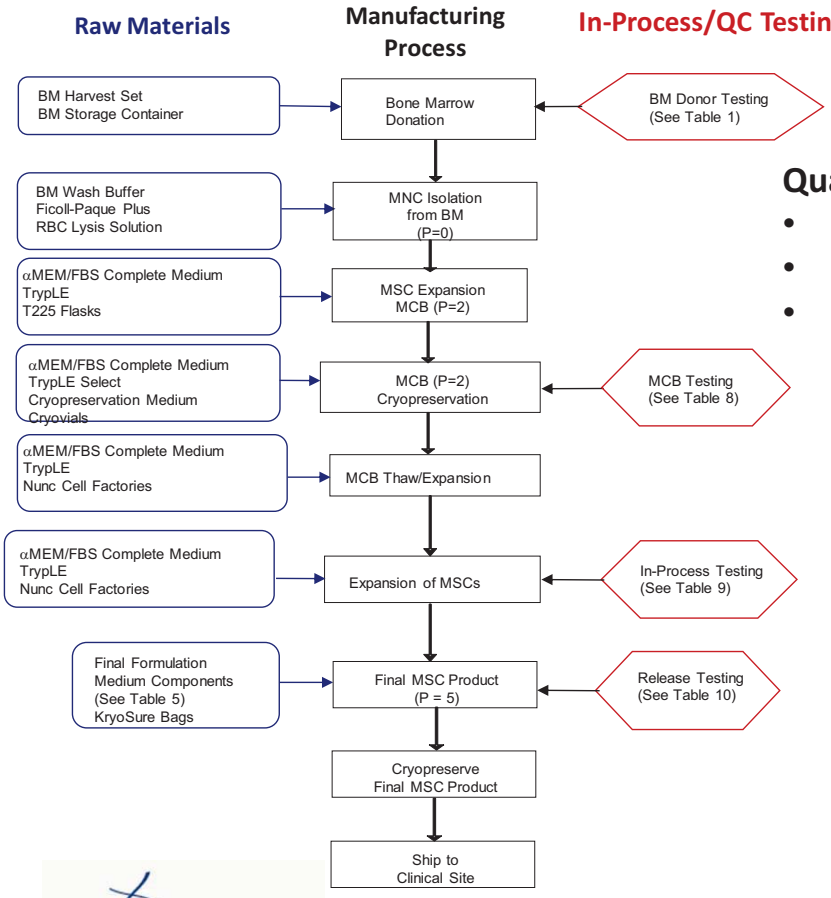

Quality System Documentation

- RM specifications
- Manufacturing batch records
- Quality Control procedures

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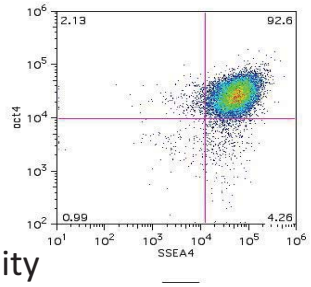
Development of the Quality Control Plan



- Raw material testing
  - Master/Working Cell Banks
  - Critical and highly variable raw materials
- In-process QC testing
  - Rapid test method for assess in-process product quality
  - Assays for key impurities – contamination cells, process impurities
- Final product QC testing
  - Standard QC methods – cell count, sterility, mycoplasma, endotoxin…
  - Product-specific assays – flow cytometry…
  - Potency assay
- Assay qualification and validation
  - Aseptic processing
  - Qualification trials
  - Process validation – Phase 3

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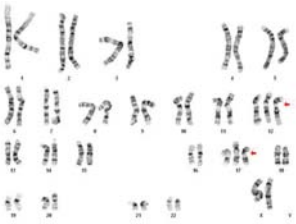
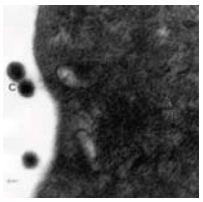
Cell Bank Characterization

- Post thaw recovery (count/viability)
- Identity – Short Tandem Repeat (STR), HLA typing
- Growth characteristics – doubling time, morphology
- Contamination - bacteria, fungi, mycoplasma
- Karyotype – G-band
- Flow cytometry for appropriate cell surface markers
- Adventitious agent testing –
  - Human – PCR for HIV, HTLV, HBV, HCV, EBV, CMV…
  - Murine – Murine Ab production, retroviruses
  - Bovine and porcine – cell culture assay
  - *In vivo/In vitro* assays for additional pathogens
- End of Production studies – impact of passage number on genetic stability and differentiation properties





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Summary of QC Testing for MSC MCB and Final Product

Test	Test Method	Specification	MCB	FP
Cell Count	Viable cell count	2-6 x 10^6/mL > 70% Viable	X	X
Identity	HLA or STR Testing	Report Profile	X	X
Sterility	Direct transfer method, 21 CFR 610.12	No contamination detected	X	X
Mycoplasma	PTC method – direct culture and Vero culture with Hoechst stain	No contamination detected	X	X
Karyotype	G-band analysis 20 metaphase spreads	Normal	X	X
Flow Cytometry	Positive: CD105, CD73, CD90 Negative: CD34, CD45, CD14, CD19, HLA-DR	Positive > 95% Negative < 5%	X	X
Adventitious Agents	*In Vitro* Adventitious Agent Testing – MRC-5, Vero, HeLa cells	No contamination detected	X	
Endotoxin	Kinetic Turbidometric LAL assay	< 2.5 EU/mL		X
Residual FBS	BSA ELISA assay	Report Value		X
Potency	**T-Cell Proliferation Assay**	TBD		X
Potency	**Cytokine/paracrine factor expression assay**	TBD		X

Establishing a Potency Assay

- Potency assay development
  - Based on hypothesized mode of action – replacement of dead/diseased cells, secreted factors (ELISA), immunomodulatory properties
  - Correlate assay data with *in vivo* performance
- Development timeline
  - Establish early in program based on hypothesized mode of action
  - Goal of establishing assay and validating by Phase 3 clinical trials
- Reference Standard
  - Create reference standard prior to initiating assay development
  - Use to establish assay characteristics- accuracy, precision…
  - Monitor stability of standard
- Process development support
  - Impact of donor variability on product quality
  - Screening of raw materials (e.g., FBS)
  - Evaluation of process changes and scale-up on product quality

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Cell Therapy Formulation and Storage

- Fresh vs. cryopreserved final product
- Additional processing prior to administration
  - Thawing, washing, additional culturing…
  - Additional QC testing and validation studies required
- Optimization of cryopreservation process
  - Container format – vials, bags…
  - Optimize cryopreservation medium, minimize DMSO
  - Optimize freezing profile
- Shipping and stability studies
  - Recovery and quality of product under standard shipping conditions
  - Thaw, process, and hold under anticipated clinical conditions

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Moving Through Clinical Trials - Future Challenges

- Continued development of potency assays
  - Look at additional markers for cell potency
  - Develop indication-specific assays
  - Establish relationship with *in vivo* performance
- Scale-up of cell manufacturing process
  - MSC dosing example – 2-6 E8 cells/dose
  - Cell Factories vs. HYPER Stacks vs. novel bioreactors
  - Cell harvest and washing methods - TFF
  - Media - identify alternative formulations to enhance cell production and process reproducibility
- Validation studies
  - Process validation studies
  - QC method validation – complete by Phase 3

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Technology Transfer Out

- Support for Investigation New Drug (IND) application –
  - Chemistry, Manufacturing & Control (CMC) write-up including data from clinical production trials
  - Waisman Biomanufacturing Facility Master File
- Phase 3 – transfer to facility for future commercial production
- Technology transfer –
  - Process and QC assay development and qualification reports
  - Production batch records with all data
  - Project-specific QC test methods
  - Technical support for transfer to 3rd party

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