Product Testing & Release

PACT Workshop: Design & Operation
of GMP Cell Therapy Facilities

April 4th/5th, 2006

Molecular&Cellular Therapeutics
University of Minnesota

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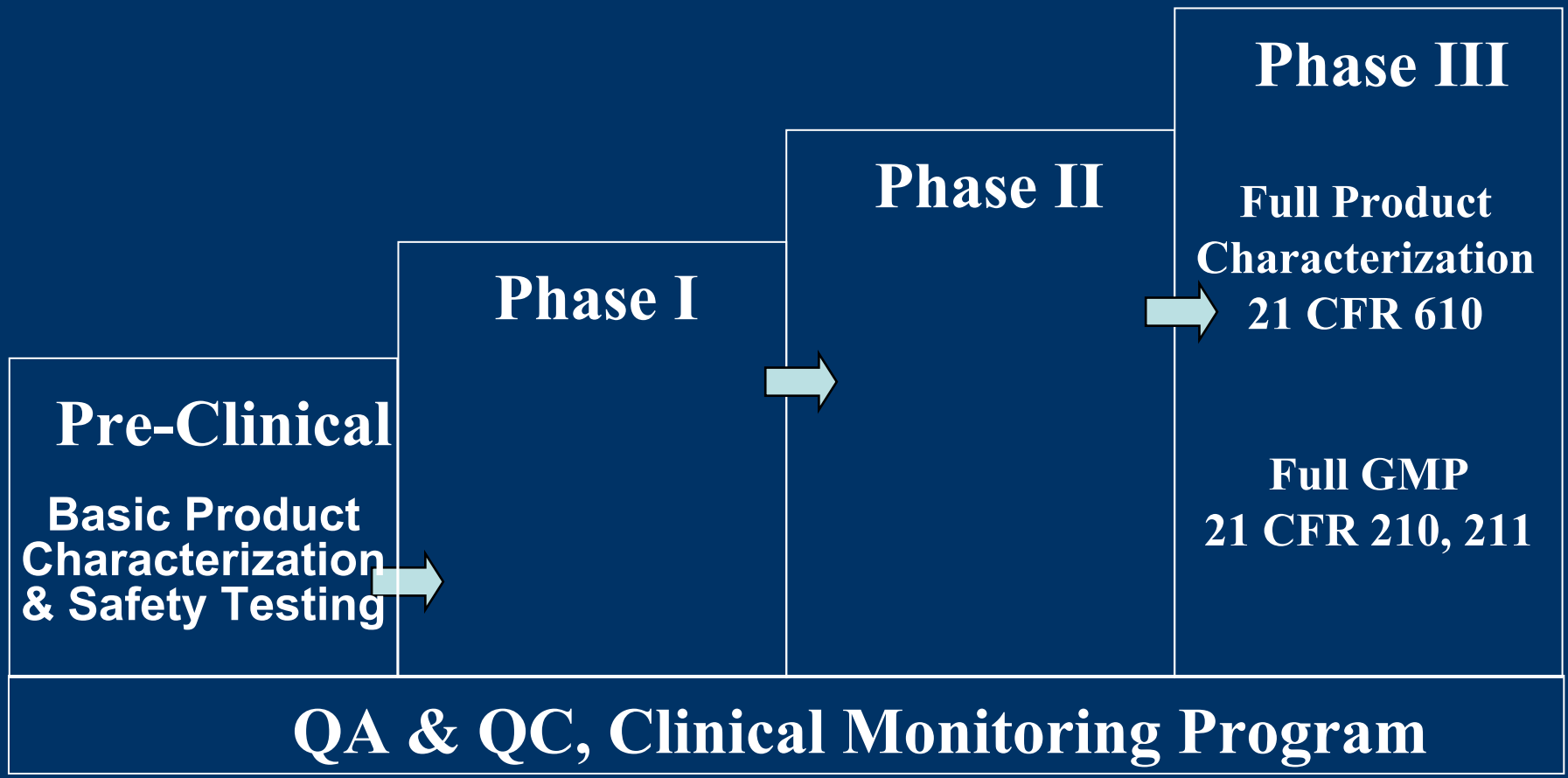
Product Testing

- Used to determine…
  - Safety, Purity, Identity, Potency, etc.
    - Suitability of the product for the individual
    - Adequacy of laboratory practices

Fulfillment of Regulatory Requirements…



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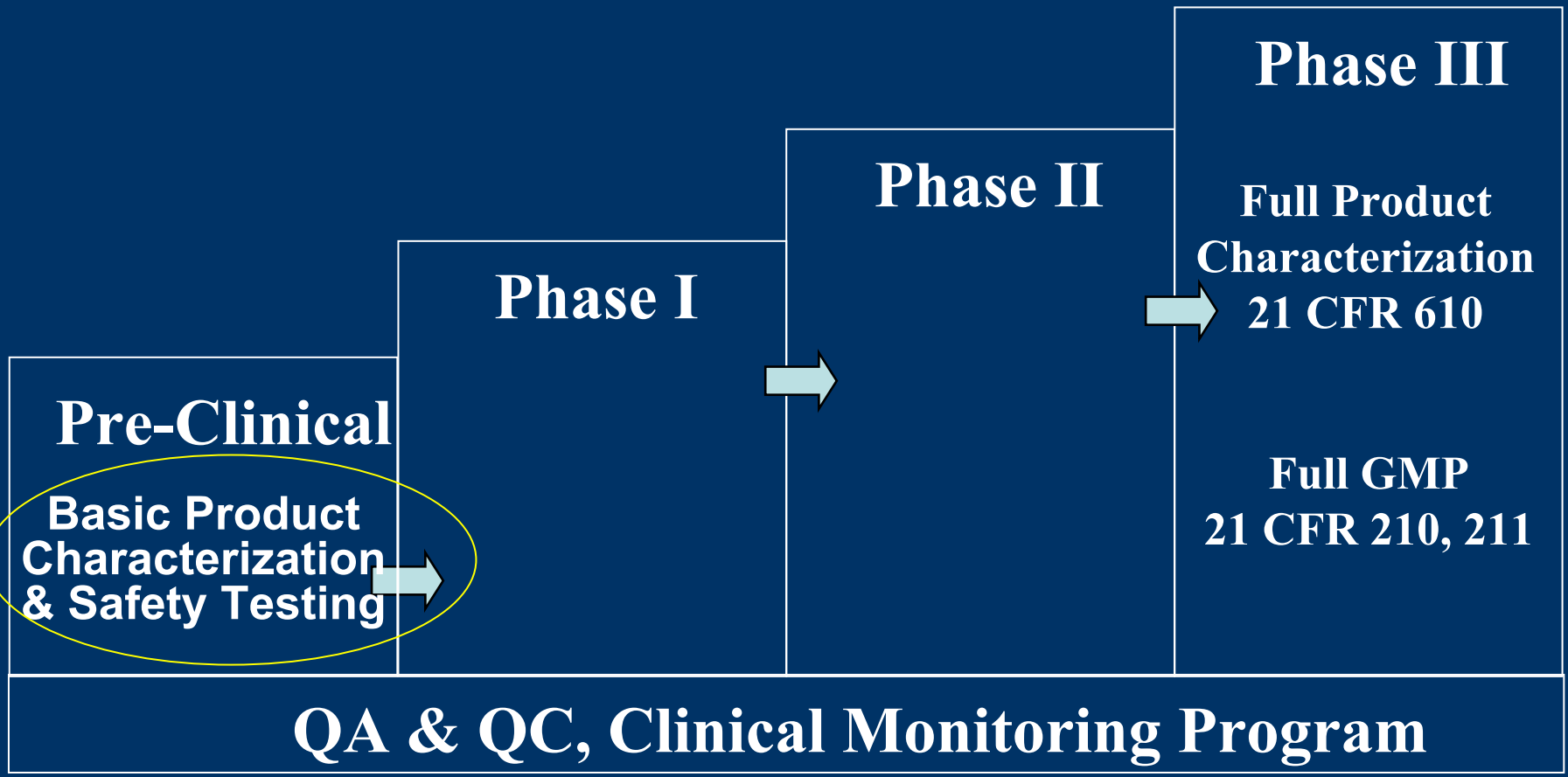
Fulfillment of Regulatory Requirements…



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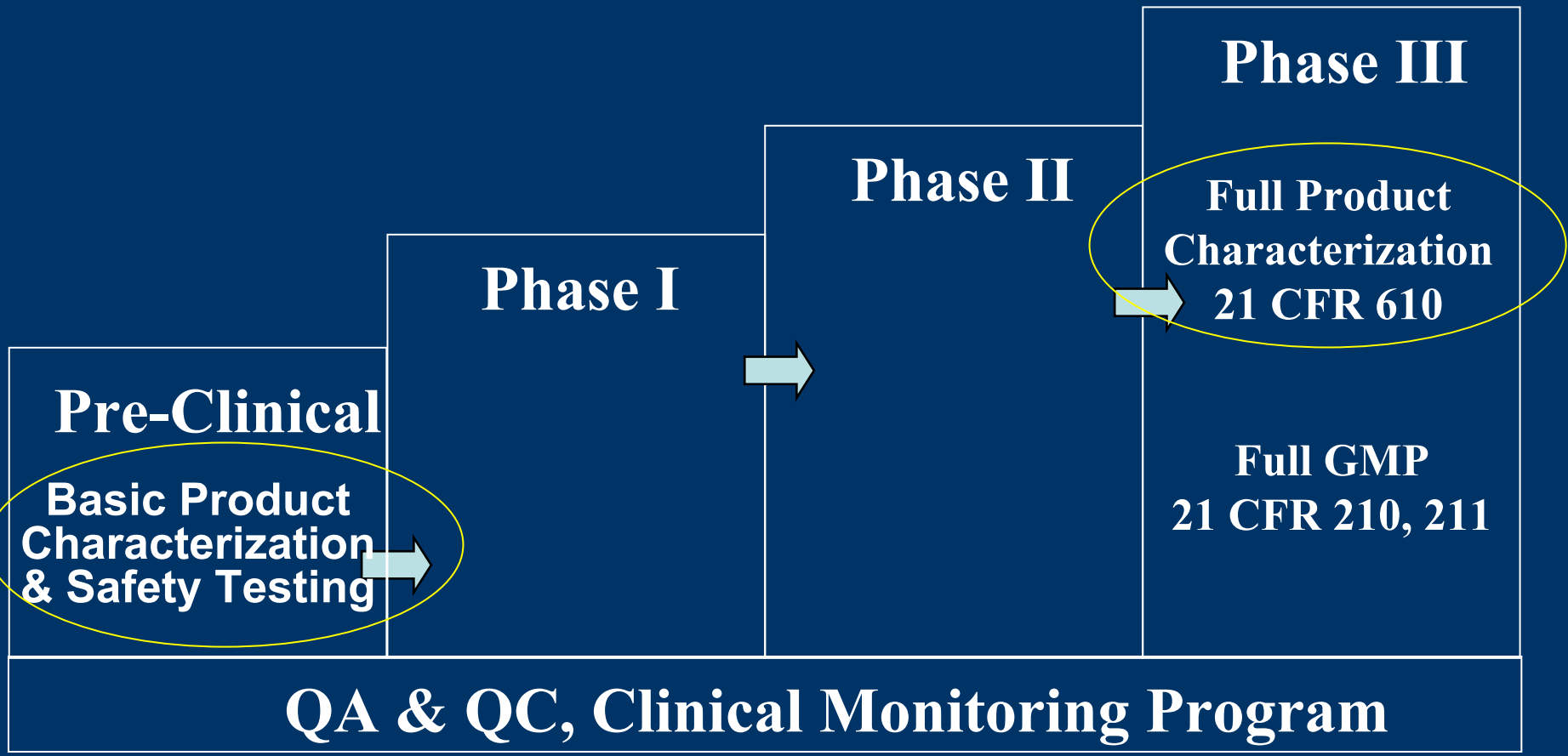

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Guidance for Industry

INDs – Approaches to Complying with CGMP during Phase I

"For known safety-related concerns, specifications should be established and met. For some product attributes, all relevant acceptance criteria may not be known at this stage of product development. This information will be reviewed in the IND submission."

Part 610 – General Biological Products Standards

§610.1 Tests prior to release required for each lot.

"No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product."

Product Testing	Example Method(s)
Microbiological Testing	
-Sterility (Bacterial & Fungal)	USP<71>, 21 CFR 610.12, Bactec*
-Gram Stain	Routine
-Mycoplasma	21 CFR 610.30, PCR-based*
-Adventitious Viral Agents	*In vitro* (indicator cell lines), *In vivo* (animals), PCR
Identity	HLA, flow cytometry, ABO/Rh, genetic polymorphisms
Purity	Endotoxin (e.g., LAL*), assays for residual extraneous material (e.g., cells, cytokines, antibodies)
Potency	Assays for biological function (in vitro, in vivo)
Other	
-Viability	Trypan blue, AO/PI, flow cytometry
-Cell Number/Dose	Cell counter, hematology analyzer
Stability	As noted above after short- and long-term storage

*May be used for early phase IND products; equivalency to 21 CFR +/or demonstration of adequate sensitivity/specificity performed by phase III/licensure.

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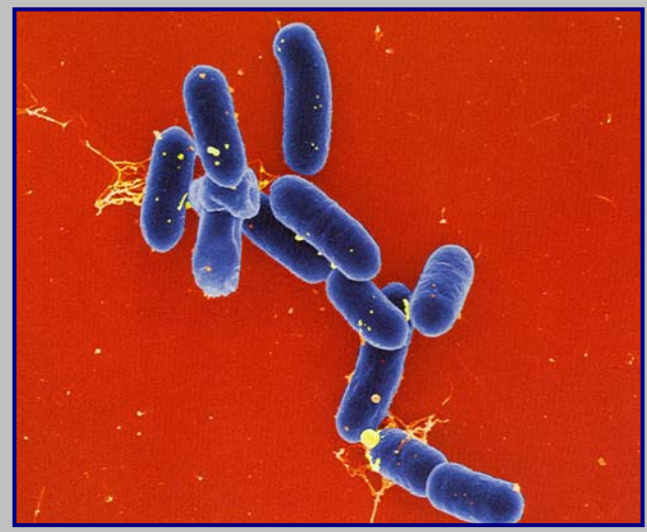
Microbiologic Testing - 1

- Primary safety testing

<u>Sterility</u>:



- Test time
- In process and final product, as appropriate
- 21CFR, USP, Bactec* (or other clinical lab method); 14 days
- *Equivalency to 21 CFR 610.12 required prior to licensure
- Khuu H, et al.¶

¶Comparison of automated culture systems with a CFR/USP-compliant method for sterility testing of cell-therapy products. Cytotherapy (2004); 6 (3): 183-195.

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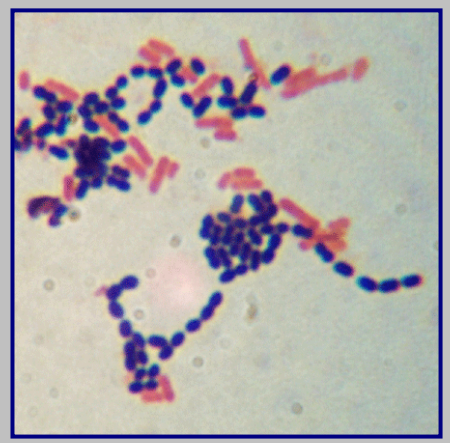
Microbiologic Testing - 2

Gram Stain:

- Questionable sensitivity with cell therapy products
- Still expected by FDA as a rapid turn–around test



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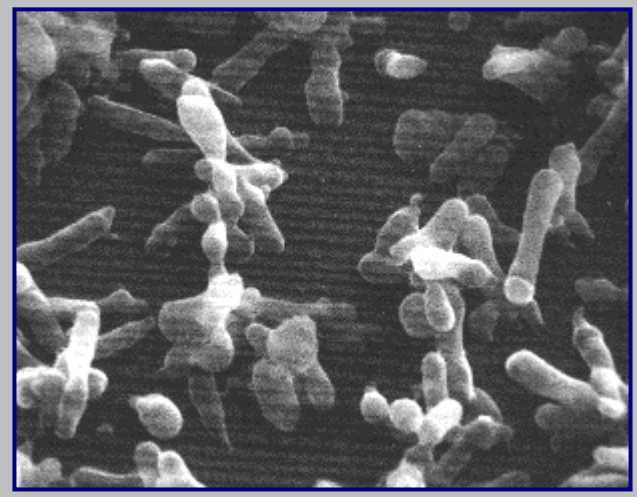
Microbiologic Testing - 3

Mycoplasma:

- Source (cells, supernatant)
- Best timing (final product, in-process)
- Culture vs. PCR (prior to licensing, demonstrate adequate sensitivity and specificity)



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Microbiologic Testing - 4

Adventitious Viral Agents:

- Variable depending on cell type/source and manipulation (gene transduction, etc.)
- See example (melanoma cell line)

Identity - 1

- Identify and distinguish from other products in lab (physical/chemical characteristics, inspection (macro/micro), specific cultural tests, in vitro/in vivo immunological tests (21 CFR 610.14)
  - HLA (serology/DNA)
  - Flow cytometry
  - ABO/Rh
  - Genetic polymorphisms

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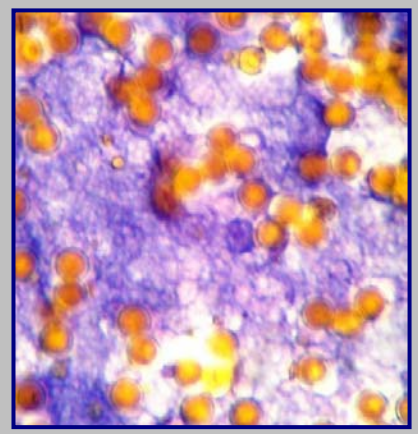
Identity - 2

- Examples:
  - Non-IND: UCB without attached segment -
    - Rapid HLA typing (serology)
  - IND: NK cells (typically only one such product processed per day) -
    - Immunophenotype (flow cytometry)
    - ABO/RH, rapid HLA type (serology) as back-up

Purity - 1

- “Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application.” (21 CFR 610.13)
- Examples of residual contaminants include:
    - Contaminating cell phenotypes/debris (CD3/CD28 bead removal with MaxSep)



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Purity - 2

- Endotoxin (typically LAL assay method)
  - Equivalency to Pyrogenicity Testing [21 CFR 610.13(b)] for licensure
  - Upper limit per FDA 5 EU/kg body weight/dose (intra-thecal lower, 0.2 EU)
  - Gel, colorimetric
  - PACT Project: EndoSafe

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Potency - 1

- “The word potency is interpreted to mean the specific ability or the capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.” [21 CFR 600.3(s)]

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Potency - 2

- In vitro/in vivo tests to satisfy potency requirement
- Examples:
  - Non-IND: HSCs –
    - CFU (or surrogate, like CD34+ cell enumeration)
  - IND: NK cells –
    - Cytotoxicity [e.g., chromium release, flow cytometry-based (e.g., Cytoxilux)]

      MSCs –
    - Differentiation assays

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Viability

- Typically acceptable by FDA ≥ 70%
- If lower, provide rationale and support indicating lower viability will not affect safety or efficacy
- Examples:
  - Flow cytometry (e.g., 7-AAD)
  - AO/PI, TB

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Cell Number/Dose

- Include minimum # of viable/functional cells
- Document if maximum dose established and how
- Examples:
  - Cell counter +/- flow cytometry
  - Viable cell counter

Stability

- Is product stable for time period required to support study?
- Use previously mentioned testing to establish stability
- Examples:
  - Cryopreserved [pre-freeze vs. post-thaw (immediate and over time)]
  - Fresh [time of final product formulation vs. time of infusion (possibly several add'l time points)]

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Final Product Release Criteria Testing

- Include in CMC
- Final product formulation for patient administration
- Each lot = each product in many (most) cases of cell therapy products
- Final test results available prior to release for administration
- Add'l results not available prior to release (e.g., sterility)
  - Include reporting procedure if post-release testing result not acceptable

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References

- 21 CFR Part 610 – General Biological Products Standards
- Guidance for Industry INDs – Approaches to Complying with CGMP during Phase I [Jan. 2006]
- Guidance for Reviewers Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) [Aug. 2003]

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Thank You

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