Early Phase Cell Therapy Product Development: Quality Management

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PACT Production Assistance for Cellular Therapies
National Heart Lung and Blood Program

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Agenda

- Definition- Cell Therapy
- Regulations- Pre clinical studies
- Issues noted by FDA during Pre-clinical studies
- Quality Management/Quality System
- Conclusion

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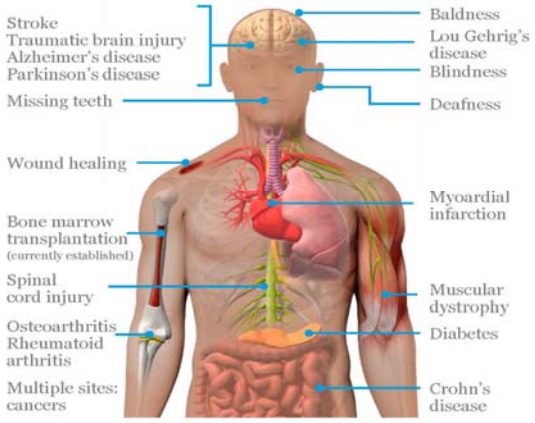
Cell therapies



Catapult –Cell and Gene Therapy

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What Regulations Govern Preclinical Studies?

21 CFR 312.20 Subpart B: IND Application

☐	Form FDA 1571	21 CFR 312.23(a)(1)
☐	Table of Contents	21 CFR 312.23(a)(2)
☐	Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
☐	Investigator's brochure	21 CFR 312.23(a)(5)
☐	Protocols	21 CFR 312.23(a)(6)
☐	Chemistry, manufacturing, and control data	21 CFR 312.23(a)(7)
☑	**Pharmacology and toxicology data**	**21 CFR 312.23(a)(8)**
☐	Previous human experience	21 CFR 312.23(a)(9)
☐	Additional information	21 CFR 312.23(a)(10)

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What Regulations Govern Preclinical Studies?

- Pharmacologic & Toxicologic Studies

  "[a]dequate information about the pharmacological and toxicological studies…on the basis of which the sponsor has concluded that it is reasonable safe to conduct the proposed clinical investigations.

  IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]

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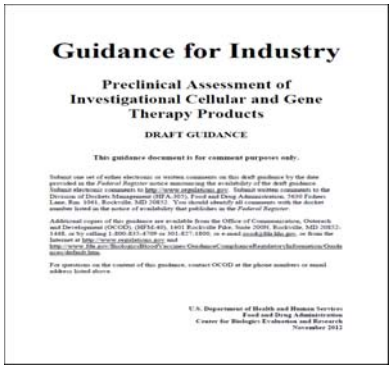
Guidelines


Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

DRAFT GUIDANCE

This guidance document is for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2012

FDA
U.S. Food and Drug Administration


INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

M3(R2)

Current Step 4 version
dated 11 June 2009

This guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA.

ICH

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Expectations of FDA from Preclinical Data

- To support a rationale for the first-in-human clinical trial
  - For cell therapy product the trial is conducted in the disease population, not in healthy volunteers
- To make recommendations regarding clinical trial design
  - Initial safe starting dose, dose-escalation scheme, dosing schedule, organ toxicity, eligibility criteria, clinical monitoring
- To meet regulatory requirements
  - 21 CFR 312.23 (a)(8)
  - 21 CFR 58 (GLP compliance)

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21 CFR Part 58:Good Laboratory Practice (GLP)

- Describes good practices for non-clinical lab studies that support research or marketing approvals for FDA-regulated products.
- Provides framework for conducting well-controlled studies
  - Assures quality and integrity of the data
  - Facilitates study reconstruction
  - Provides overall accountability

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GLP: Scope

- Nonclinical safety data is the first step in identifying possible safety concerns

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Issues noticed by FDA during GLP inspections

- Data integrity and Study conduct
  - Data falsification
  - Lack of GLP compliance
  - Study Directors don't always know if the intended dose was actual dose administered
  - Single point of study control
    - Overall responsibility for technical conduct of study, interpretation, analysis, documentation, reporting of results

Issues noticed by FDA during GLP inspections

- Study Director
  - Signed the final report before receiving the results
- Test article in Controls
  - Dosing error?
  - Sample contamination?
  - Testing error?

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Issues noticed by FDA during GLP inspections

- Study personnel with less training than counterparts at other facilities
  - Impact: Studies performed unreliable for review purposes.

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Quality Management

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Quality Assurance (QA)

- Inspect each non clinical laboratory study at regular intervals.
  - Assure the integrity of the study and maintain written documentation.
  - Written records are in place and in sufficient detail so the study can be reconstructed.
  - Review Training documentation of personnel.
  - Inspect equipments to ensure they are properly maintained and calibrated.
  - Review reagents and materials used for testing.

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Quality Assurance (QA)

- Review Study Plan.
- Changes to protocols.
- Report any inspection results to management.

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Quality Assurance

- Review study final study report.
  - Results accurately reflect the raw data.
- Statement whether study was conducted in compliance to GLP provided in the final study.

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Conclusion

- Pre clinical studies for cell therapy are significantly different from traditional small molecule studies or medical devices.
- All pre-clinical studies must be performed under GLP compliance.
- Quality system must be in place to ensure the study is conducted as per the regulations and the study can be reconstructed.