US Regulation of Cell and Gene Therapy Products

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US FDA CBER and CDRH Regulate Cell Therapy, Gene Therapy, and Tissue-Engineered Products

• FDA-CBER Office of Cell, Tissue, and Gene Therapy (OCTGT)
  – Human Cell, Tissues and Cellular and Tissue-Based Products (HCT/Ps)

• May be regulated as Biologics, biologics/device Combination Products, sometimes as Devices
  – IND or IDE pathway to BLA, 510K
  – FDA CBER for Biologics
  – FDA CBER/CDRH for Combination Products, CBER typically primary Center
US FDA Office of Cell, Tissue and Gene Therapy (OCTGT)-Regulated Products

- Cell therapy products
- Gene therapy products
- Tumor vaccines and immunotherapy products
- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
- Tissue and tissue-based products
- Cell- or tissue-based combination products
  - Cell/device, tissue/device, other
- Devices used for cells/tissues
  - Processing devices, other
- Xenotransplantation products
- Donor screening tests (cadaveric blood samples)
Regulation is Risk-Based

• Cell therapy, gene therapy, and tissue-engineered products are complex living biologics, and are being developed in novel, evolving ways. Regulation of these products commonly reflects their novel, diverse nature.

• Regulations define criteria for product safety, identity, purity, potency, and clinical efficacy.

• FDA follows a science-driven, risk-based approach in evaluating whether and how these criteria have been met.

• Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.
FDA’s Risk-Based Regulatory Framework for Cell and Gene Therapy Products

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<table>
<thead>
<tr>
<th>Lower Risk, “361” Products</th>
<th>Higher Risk, “351” Products</th>
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<tbody>
<tr>
<td>Comparatively simple, well-understood products, low-risk applications</td>
<td>More complex, novel biologic products, higher-risk applications</td>
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<tr>
<td>• Minimal manipulation, homologous use only, not combined with another article, no systemic effect (with some exceptions)</td>
<td>• Does not meet all criteria for a “361” product</td>
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<td>• Cells expanded ex vivo, gene-modified, activated, etc.</td>
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# FDA Requirements - GMPs, GTPs, GCPs

<table>
<thead>
<tr>
<th>Good Manufacturing Practices (GMPs)</th>
<th>Ensure consistent manufacture of safe, pure, potent products</th>
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<tbody>
<tr>
<td>Good Tissue Practices (GTPs)</td>
<td>Prevent infectious disease transmission</td>
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<tr>
<td></td>
<td>Donor screening and testing</td>
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<tr>
<td></td>
<td>Prevent cross-contamination, mixups</td>
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<tr>
<td></td>
<td>Product recovery, processing, storage, labeling, distribution</td>
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<tr>
<td>Good Clinical Practices (GCPs)</td>
<td>Ethical, scientific quality standards</td>
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<tr>
<td></td>
<td>Protect trial subjects rights, safety, confidentiality</td>
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<td></td>
<td>Assure credibility of clinical trial data</td>
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## Application of FDA Regulatory Requirements

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<thead>
<tr>
<th></th>
<th>361 HCT/P</th>
<th>351 HCT/P</th>
<th>Device</th>
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</thead>
<tbody>
<tr>
<td><strong>Tissue</strong></td>
<td>361 PHS Act</td>
<td>361 PHS Act, 351 PHS Act, FD&amp;C Act</td>
<td>FD&amp;C Act</td>
</tr>
<tr>
<td><strong>Applicable Laws</strong></td>
<td></td>
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<tr>
<td><strong>Applicable Regulations</strong></td>
<td>21 CFR 1271</td>
<td>21 CFR 1271, 21 CFR 600’s, 21 CFR 200’s, 21 CFR 300’s</td>
<td>21 CFR 800’s</td>
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<tr>
<td><strong>Marketing Pathway</strong></td>
<td>Premarket review not required</td>
<td>BLA</td>
<td>PMA, 510(k), HDE</td>
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Regulatory Considerations in Product Development

Product development stage determines key aspects of regulatory review. Safety is a consistent, critical focus throughout product development.

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US FDA OCTGT
Development Throughout Clinical Trials

• FDA expects ↑ control as clinical development progresses
  – Manufacturing, characterization, specifications refined based on experience

• Early-stage trials and manufacturing must be sufficiently controlled to enable clinical development to licensure
  – The nightmare scenario: the therapy works, but inadequate understanding of the product impedes further clinical progress
Regulatory Interactions and Submissions

- FDA
  - Pre-Pre-IND meeting
    - Emphasizes preclinical pharmacology/toxicology and initial clinical trial plans
    - See separate file, Pre-Pre-IND Briefing Document Elements
  - Pre-IND meeting
    - Formal meeting or teleconference with FDA, to address questions or concerns prior to preparing IND application.
  - IND application
    - Preclinical pharmacology/toxicology
    - CMC (manufacturing and testing)
    - Clinical

- NIH RAC
- IRB
Interactions With FDA Throughout Product Development

- Pre-IND/IDE Phase
  - Preclinical Development
    - Pre-IND/IDE Meeting (Informal)
  - IND Application
  - IND/IDE Review Phase
  - Clinical Trials Phase I - II - III
    - End of Ph 2 Meeting
    - FDA must review IND within 30 days
  - License Application (BLA)
    - Pre-BLA/PMA Meeting
  - Marketing Application Phase
  - Post-marketing Phase
  - Marketed Product
    - Safety Meetings
    - Post BLA Meeting

Adapted from http://www.fda.gov/Cder/genomics/pharmaconcept/n.pdf
Pre-Pre-IND Checklist

• Emphasis on preclinical pharm/tox, and clinical trial plans. Address key aspects of review at this stage.
• Description of the intended clinical product
• Manufacturing and testing (CMC)
  – Manufacturing process flow diagram and description, show sampling points
  – Raw materials table - materials used, quality, source, ancillary material or excipient
  – Proposed in-process and release testing - safety, purity, identity, potency, stability
• Outline of proposed clinical trial
  – Subject population
  – Dosing levels and regimen
  – Route of product administration
  – Dosing procedures
  – Parameters to be assessed
• Summary of preclinical data to date
  – Activity/prooﬁng of concept
  – Toxicity/safety
  – Immunology
  – Relevant publications
  – Detailed discussion, outline of each additional planned study to assess safety of product in humans
• Specific questions about pharm/tox aspects of pre-pre IND package
Pre-IND Checklist - I

• More extensive than Pre-Pre-IND briefing document. Should describe manufacturing and testing in greater detail, and address plans for patient monitoring and follow-up.

• Product information
  - Description of product, intended use, clinical application
  - Description of the vector (if any) and vector derivations
  - Description of the delivery device, if applicable

• Manufacturing and testing (CMC)
  - Manufacturing scheme – outline and description
  - Raw materials – source, grade, qualification
  - In-process testing - steps, process-continuation criteria
  - Release testing – safety, identity, purity and potency
  - Final formulation, specifying excipients and container
  - Stability – describe stability studies and specifications
  - Description of manufacturing site(s) and QA/QC system
Pre-IND Checklist - II

• Product use
  – Transport and storage descriptions, specifications, tracking system
  – QA/QC system at clinical site(s)
  – Description of product administration procedure

• Preclinical information and discussion based on outcome
  – Summary of all *in vitro* and *in vivo* preclinical studies, with results and interpretation
  – Rationale for proposed therapy, discussion of proof of concept, evidence that product has desired biologic effect
  – Dosing
    • Dose/activity and dose/toxicity relationship
    • Proposed initial safe dose, dose escalation scheme(s) for clinical study
  – Toxicity
    • Type, frequency, and severity of toxicities in normal animals and disease model(s)
    • Potential clinical toxicities, projected risks, organ(s) affected, indicators
  – Relationship of route of administration and dosing regimen to product efficacy and toxicity
  – Risk evaluation - significance and severity of observed toxicities/adverse findings compared to other disease-related adverse events
Pre-IND Checklist - III

• Preclinical studies yet to be performed, for results to be included in IND
  – Detailed outline of study designs

• Proposed clinical study design including
  – Target indication
  – Objective
  – Sample size
  – Study site location(s)
  – Patient eligibility criteria, key inclusion and inclusion criteria
  – Dose(s) and route(s) of administration, procedure
  – Concomitant medications and treatments
  – Outcome measures
  – Data analysis plan
  – Safety monitoring plan
  – Termination criteria
Elements of the IND Application

- Preclinical
  - Activity, efficacy, safety studies
  - Localization/distribution
- CMC (manufacturing, testing)
  - Manufacturing process, facility
  - Reagents and other raw materials
  - Testing – patient, product
- Clinical
  - Trial plan, patient population, inclusion/exclusion criteria, dosing
  - Outcomes, monitoring, informed consent
Characterization Testing - US FDA Requirements

• Based on 21 CFR 610
• Safety
  – Sterility, mycoplasma, adventitious agents
  – Tumorigenicity
• Purity, Identity
  – Measure intended product components, as well as contaminating cells and other undesired agents, including endotoxin.
  – Reagents/ancillary materials, excipients
• Potency
  – Relevant biological function(s). May require a matrix of functional and nonfunctional assays.
• Stability

Characterization is expected to improve as clinical development progresses, but analytical rigor is needed from the outset
Combination Products

• Administering cells with certain specified devices, or seeded onto scaffolds, can trigger regulatory evaluation as a combination product
  – Cells regulated under Biologics/Drug regulations, device regulated under Device regulations

• Discuss regulatory pathway with FDA, and with Device manufacturer
• Establish cell-device compatibility
• Include cells and device in preclinical studies
• Establish and qualify administration procedure, and clinician-investigator training
Questions to address for successful IND

- What type(s) of cells will be used, and what is the source?
- What is the projected dose? How many cells are needed to achieve a minimum/optimal biological effect?
- Have the cells been sufficiently characterized for the stage of clinical development?
- What is the proposed mechanism of action?
- Is cell survival/engraftment necessary?
- Is repair or replacement of damaged tissue the goal?
- Hypothesized cell fate following administration?
- Will the product be administered as a suspension? Seeded onto a scaffold? Encapsulated?
- Will immunosuppression be needed?
- What is/are the biologically relevant animal species for preclinical studies?
- Are there potentially relevant animal models of disease/injury that can be used?
- What is the optimal method/route/anatomical site/timing for product administration?
- **What is the risk/benefit balance?**
Comparability – Product Used in Preclinical Studies vs. Clinical Product

• Manufacturing process
  – Should be as similar as possible for the cell therapy product used in preclinical studies and the clinical product
  – Tissue/cell harvest, cell isolation, selection, activation, gene modification, expansion, formulation/scaffold seeding, encapsulation, storage conditions, etc.

• Characterization testing combination product
  – Assess comparability of data for preclinical and clinical products
  – Emphasis on identity testing and, to the extent possible, potency
    • Cellular morphology and phenotype
    • Molecular/biochemical markers
    • Functional assays
Risk Assessment/Management Tools

- Quality by Design (QbD)
- Failure Mode and Effect Analysis (FMEA)
  - Particularly useful for cell therapy, tissue-engineering processes
- Problems, mistakes, and failures are valuable indicators of process weaknesses.
- Deviation reports are tools for process improvement.
  - Productive mistake-making

Guidance for Industry
Q9 Quality Risk Management

Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products

A Quality Risk Management Model Approach for Cell Therapy Manufacturing

www.ac-gt.com
Failure Mode and Effect Analysis (FMEA)

• Define process steps
• Failure Mode identification
  – Ways in which a product or process could fail to perform intended function, at each step
  – Possible causes and effects of failure
• Failure Mode rating
  – Severity – consequences of failure
  – Probability of failure
  – Detectability – likelihood of detecting failure
• Criticality analysis, assigns priorities for each failure mode
  – Risk Priority Number = Severity × Probability × Detectability
• Identify and perform actions to mitigate risk
• Ongoing monitoring and follow-up
Common Causes of Hold Actions
Phase 1, Cell and Gene Therapy

• Insufficient preclinical information to assess patient risk
  – Lack of preclinical safety data, Insufficient safety data to support starting dose, incomplete safety study reports, insufficient product characterization

• Inadequate preclinical study design
  – Safety monitoring (safety/activity endpoints), animal number, study dose and duration, route of administration

• Insufficient preclinical data to support safety of administration to humans

• Product to be used in trial differs from that used in preclinical studies

• Dose escalation scheme is too aggressive

• No information about compatibility of product and delivery device

• Inadequate clinical monitoring plan to observe potential toxicities

• Inappropriate patient eligibility criteria

• *The potential benefits do not outweigh potential risks*
Common Causes of Hold Actions
Phase 1, Cell Therapy

• Manufacturing
  – Absent or inadequate manufacturing description
  – Research-grade ancillary reagents inadequately qualified
  – Bovine-derived components inadequately qualified
  – No description of tracking and segregation procedures to assure patient receives correct cells
  – Segregation and cleaning procedures inadequately described
  – Inadequate QA/QC program

• Testing
  – Inadequate lot release testing
  – Cells do not meet minimum viability criteria of 70%
  – No action plan for positive sterility test after administration
  – Donor virus testing - inadequate or inappropriate tests
  – Incomplete human pathogen testing (human cell lines)
  – No tumorigenicity testing
Common Causes of Hold Actions
Phase 1, Gene Therapy

• Manufacturing and Testing
  – Vector sequence not provided
  – No *in vitro* adventitious agent testing of final vector product, or incorrectly performed *in vitro/in vivo* adventitious agent testing
  – Incomplete human pathogen testing on human cell lines
  – Inadequate QA/QC program
  – Segregation and cleaning procedures inadequately described
    • Prevent cross-contamination from production of multiple vectors
  – Inadequate lot release testing
    • RCR assays, endotoxin, sterility testing
Common Causes of Hold Actions
Post-Phase 1, Cell and Gene Therapy

• Critical assays (potency, identity, other) are not...
  – ... validated, reproducible, quantitative, sensitive, specific, biologically relevant
• Stability program inadequate, unsuitable, or absent
• Characterization data insufficient to establish lot release specifications
• Comparability not adequately demonstrated
• Safety issues
  – High levels of bioburden resulting from contamination
BLA Issues

• *Significant* change(s) made late in development, without adequate product comparability data
  – Viral clearance evaluation studies may be needed
• Process validation data incomplete, inadequate, or absent
• Inadequate stability studies
• Characterization data inadequate to support establishing specifications
• Consistent manufacturing inadequately demonstrated
• Compliance issues - contract manufacturers, finish and fill facilities
Regulatory Considerations for Initiating Clinical Trials

- Risk/Benefit – clinical trial subject safety is balanced against potential public health benefits of novel therapies.

- Risk assessment based on:
  - Product characterization data and preclinical data supporting safety
  - Product administration procedure, dose levels, dosing scheme
  - Patient eligibility criteria
  - Parameters to monitor clinically, safety monitoring plans, follow-up
Key Points to Enable Progress to Clinical Trial

- Dosing!
- Minimum effective dose
  - Single or multiple administrations?
- Route/mode of administration
  - Effect of any surgery on interpretation
- Sustained efficacy, if applicable
- Blinding
- Long-term follow-up
References and Resources

• Guidance for FDA Reviewers and Sponsors: Content and Review of CMC Information for Human Somatic Cell Therapy INDs (www.fda.gov/cber/gdlns/gtindcmc.htm)

• BSI PAS 93 - Characterization of Cell Therapy Products, 2011 (draft)

• Assay Validation International Conference on Harmonization; Validation of Analytical Procedures: Methodology; Q2B, 1996 (www.fda.gov/cder/guidance/ichq2b.htm)

• ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

• USP Chapter <1046> Cell and Gene Therapy Products

• USP Chapters <111, 1030, 1032, 1033, 1034> Biological Assays

• USP Chapter <1098> Validation of Test Kits


• EMEA CHMP Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products For the Treatment of Cancer, 2007

Standards and Standardization Efforts

- US FDA, EMA
  - Guidance documents
- USP, EP, EDQM
  - Pharmacopeial standards for reagents, ancillary materials
- ATCC
  - Cell lines, other biological standards
- ASTM Division on Tissue Engineered Medical Products
  - Biomaterials, Cells and Tissue-Engineered Constructs, other standards
- International Conference on Harmonisation (ICH)
- Foundation for the Accreditation of Cellular Therapy (FACT)
- ICCBBA, ISBT 128
- International Society for Cellular Therapy (ISCT)
- American Association of Blood Banks (AABB)
- American Association of Tissue Banking (AATB)
- American Society for Blood and Marrow Transplantation (ASBMT)
- College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA)
- Joint Accreditation Committee (with EBMT)
- International Organization for Standardization (ISO)