FDA Framework for Gene Therapy Development

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Human Gene Therapy (GT) Products

“mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host genetic sequences”

• Variety of products
  – Viral vectors
  – Bacterial vectors
  – Plasmid DNA, mRNA
  – Human genome editing products (e.g., gRNA, RNP, endonucleases)
  – Ex vivo genetically modified cells

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GT Field is Growing Rapidly

New Human GT IND Submissions (1990-2018)
Objective of FDA Review (21 CFR 312.22)

- Lifecycle approach to product development
- ... in all phases of the investigation to assure the safety and rights of subjects
- ....and in phase 2 and 3 studies, to help assure that the quality of the scientific evaluation of drug product is adequate to permit an evaluation of the drug’s effectiveness and safety
Recent CBER Guidance Documents:

• Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus during Product Manufacture and Patient Follow-up: Draft Guidance for Industry (July 2018)
• Observing Subjects Who Received Human Gene Therapy Products for Delayed Adverse Events: Draft Guidance for Industry (July 2018)
• Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Guidance for Industry (February 2019):
• Disease-Specific Guidances: Draft Guidance for Industry (July 2018)
  • Human Gene Therapy for Hemophilia
  • Human Gene Therapy for Retinal Disorders
  • Human Gene Therapy for Rare Diseases

https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm223006.htm
www.fda.gov
GT CMC Guidance

• Applicable to all GT products
  – Product class recommendations noted when applicable

• Organized into CTD format
  – Drug Substance (DS) section for vector used in manufacturing of ex vivo modified cells

• Regulatory requirements are phase specific
  – Phase 1 CGMPs
  – Product characterization and release criteria
  – Assay development, qualification, and validation
Navigating the FDA Framework During Global Development

• Align regulatory and scientific development through productive interactions
• Leverage accumulated data
Early Interactions Support Product Development

**Development**
- Preclinical

**Clinical Trials**
- Phase I
- Phase II
- Phase III

**Post-Marketing**
- BLA
- Post-Marketing

**Preclinical**
- Pre-IND Meeting
- End of Ph 1 Meeting
- End of Ph 2 Meeting
- Pre-BLA Meeting

**IND submission**

**Marketing Application**

**INTERACT**
(Informal)
(Not PDUFA VI)

**PDUFA VI**
“The Program” Meetings
Designing a Global Development Regulatory Program

Preclinical:
• IPRP Reflection Paper on Biodistribution, 2018

CMC:
• Phase-specific, align with clinical development
• Comparability between products used for early and late phase studies

Clinical:
• Historical vs. active control
• Other available therapies
• Previous treatments
• Disease-specific guidances
<table>
<thead>
<tr>
<th>Program</th>
<th>Intended function</th>
<th>Required information</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakthrough Designation (BTD)</td>
<td>To treat a serious or life-threatening disease or condition</td>
<td>Preliminary clinical evidence</td>
<td>Intensive guidance on efficient drug development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Demonstrate substantial improvement over existing therapies on ≥1 clinically significant endpoints</td>
<td>FDA Senior Management</td>
</tr>
<tr>
<td>Regenerative Medicine Advance Therapy (RMAT)</td>
<td>To treat, modify, reverse, or cure a serious or life-threatening disease or condition</td>
<td>Preliminary clinical evidence</td>
<td>All features of BTD including early interactions to discuss potential</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential to address unmet medical needs for such disease or condition</td>
<td>Potential ways to support accelerated approval</td>
</tr>
</tbody>
</table>
Special Considerations for GT Products

• Small lot size, patient-specific lots or not many clinical lots

• Clinical programs may advance rapidly and the timelines from early to late development may be compressed

• Regulatory requirements do not change

• Planning for commercial manufacturing should be conducted early (Phase 1/2)
  • Product characterization and stability
  • Understanding effects of manufacturing changes
  • Choice of potency assay and relationship to clinical outcome for licensure
GT Assay Development

For INDs, **sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency.** The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.


**Early Phase Studies:**
- Qualify assays used for product release and stability testing (suitable for the intended purpose)
- Develop characterization assays
- Explore a variety of product characteristics

**Late Phase Studies:**
- Validate critical assays (potency and dose)
- Lot release assays:
  - Validation planned or completed
- Characterization assays:
  - Developed & qualified
- Reference standards & controls:
  - Developed & qualified

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Encourage Early Product Characterization

A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. - ICH Q8 (R2)

• Explore many CQAs during early development
  • Report results early in development
  • Choose relevant tests for late phase studies

• Evaluate multiple measures of CQAs, especially potency
  • Matrix of assays
  • Orthogonal methods
  • Stability indicating

• Support comparability studies
Concurrent & Early Assay Development

Early product characterization can support assay development for key product attributes (potency, purity, identity)

Assay development

- Assay 1
- Assay 2
- Assay 3
- Assay 4

Concurrent & early assay development

Development | Qualification | Validation
--- | --- | ---
X Reject | X Reject | Validated
Validated

Product characterization
Leverage Development Across Similar Products

Develop manufacturing process and assays
Develop manufacturing process and assays
Leverage Development Across Similar Products

- Example: cross-referencing manufacturing information
- Clearly state the information you are referencing and where it is located in the file
- Referenced information does not need to be repeated; only include information specific to your product
- Submit a letter of authorization to cross reference an IND if you are not the Sponsor; referenced information remains proprietary
CBER Drug Master Files (MF)

- MF holder authorizes sponsors to rely on the MF information to support a submission to FDA without the having to disclose the MF information
- Submit directly to CBER for GT-related MFs
- DRAFT Drug Master Files Guidance for Industry (October 2019)

<table>
<thead>
<tr>
<th>Common CBER MF Type</th>
<th>Information</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Manufacturing process</td>
<td>CMO manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manufacturing and testing of a DS (e.g., vector) or reagent</td>
</tr>
<tr>
<td>5</td>
<td>Reference material</td>
<td>CMO facility description</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QA/QC information</td>
</tr>
</tbody>
</table>

CMC Changes During Development

• Manufacturing process change
• Manufacturing facility change
• Additional manufacturing facilities
Analytical Comparability Study Considerations

• Recommend making changes prior to initiating clinical studies intended to support efficacy for licensure
  – If changes are introduced in late stages of development with no additional clinical studies planned to support the BLA, the expected level of comparability demonstration will be significantly higher.
  – If analytical comparability study data are not sufficient to establish comparability, additional pre-clinical and/or clinical studies may be required to demonstrate comparability of product safety and efficacy.

• Establishing comparability allows combined analysis of efficacy data

• Comparability protocol should be developed and discussed with FDA prior to performing the comparability assessment
Challenges for Establishing Comparability

• Limited manufacturing experience:
  – Not many lots produced
  – Not enough retention or test samples available

• Limited in-process testing: process variables and CPPs not known

• Limited product characterization: CQAs not known, product and process related impurities not well characterized

• Limited assay development (e.g., purity, potency)
  – Assays not qualified or not stability indicating
  – Reference standards not established or adequately characterized
Summary

GT products are complex in composition and how they are manufactured. We recommend that sponsors:

• Align scientific and regulatory development with clinical study timeline.
• Identify the critical quality attributes of the product early in development.
• Develop a matrix approach for measuring certain CQAs of the product (in cases where it is feasible).
• Build a robust analytical tool box not only for product release testing but also for product characterization, stability testing, and in-process testing.
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