

FDA Draft Guidance: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapies

John Hyde, PhD, MD
**Office of Cellular, Tissue and Gene
Therapies**



Motivation for Guidance

- Cellular and gene therapy (CGT) products have distinctive features
- Design of early-phase trials often different than for other pharmaceuticals
- Provide perspectives to improve early development of cell & gene products
- Does not set forth new requirements

Intended Scope

- Applies to biological products for which OCTGT has regulatory authority
- Not for:
 - Tissue-based products
 - Devices
 - Biologics regulated by Center for Drug Evaluation and Research (CDER)

Timeline

- July 2, 2013: Draft guidance published for public comment
- Oct. 23, 2013: Advisory Cmte discussion
- Nov. 22, 2013: End of comment period
- Plan to finalize guidance as soon as feasible thereafter

Outline

I. Introduction

II. Background

III. Features of CGT Products

IV. Clinical Trial Design

V. Meetings with OCTGT

VI. Guidance on Submitting an IND

VII. References

Introduction and Background

I. Introduction

- Purpose and scope

II. Background

- Important early experiences
- Features of CGT products

III. Features of CGT Products

A. Product Characteristics

- General: relative lack of clinical experience; persistence; may need invasive procedures
- Cells: donors, differentiation, migration
- Genes: expression control, genome alteration, shedding
- Gene-modified cells: features of both cells and genes

III. Features of CGT Products

B. Manufacturing Considerations

- Complexity
- May be limits on concentration or doses
- Logistics, possibly short “shelf life”
- May be subject-specific
 - Variability
 - May be a significant delay between enrollment and treatment

III. Features of CGT Products

C. Preclinical Considerations

- PK generally not feasible
- Species specificity
- Immunogenicity
- Extrapolation can be challenging

IV. Clinical Trial Design

A. Objectives

B. Choosing a Study Population

C. Control Group and Blinding

D. Dose Selection

E. Treatment Plan

F. Monitoring and Follow-up

IV. Clinical Trial Design

A. Objectives

- Safety
- Dose exploration
- Feasibility
- Activity assessments

IV. Clinical Trial Design

B. Choosing a Study Population

- Healthy volunteers often not acceptable
 - Persistence, risk – may call for potential to benefit
- Disease stage or severity
 - Risk-benefit considerations – most severely affected should not be automatic choice
- Lack of other treatment options
- Pediatric subjects

IV. Clinical Trial Design

C. Control Group and Blinding

- Controls can be of value for safety and preliminary activity assessments
- Blinding helpful but less critical in early phase
- Invasive controls might not be appropriate in early-phase trials

IV. Clinical Trial Design

D. Dose Selection

– Role of preclinical data

- Allometric scaling for CGT products may be less precise than for small molecules
- Previous clinical experience with related products might be helpful

– Describing dose

- Cellular product may be a mixture of cell types
- Gene transduction rates can be highly variable

IV. Clinical Trial Design

E. Treatment Plan

- Dosing regimen
- Staggering administration
- Cohort size
- Operator training
- Patient-specific products

IV. Clinical Trial Design

F. Monitoring and Follow-up

- General considerations
 - Safety
 - Bioactivity – may be slow or delayed
- Special considerations for CGT products
 - Immunogenicity
 - Persistence
 - Migration
 - Shedding
 - Growth and development

IV. Clinical Trial Design

F. Monitoring and Follow-up (cont.)

– Duration of Follow-up

- Cover time during which product thought to present safety concerns
- For most CGT products, ≥ 1 year is appropriate
- Guidance for certain gene therapy products
- Long-term follow-up may be less detailed than in main part of study
- Follow-up after harvest even if product not given
- Special considerations for pediatric subjects

IV. Clinical Trial Design

F. Monitoring and Follow-up (cont.)

– Stopping rules

- Uncertainty about frequency or severity of adverse reactions
- May be a need to change enrollment, dosing, administration, or monitoring to mitigate risks
- “Stopping” rule not a termination rule

V. Meetings with OCTGT

- Encourages prospective IND sponsors to meet with FDA staff
- Suggests several clinical topics for discussion at a meeting

VI. Submitting an IND

- Cites regulations and other guidances concerned with the information that should be provided in an IND submission
- Brief general advice
- Suggests developing an overall development plan

Draft Guidance Comments

- Draft guidance is available in the guidance section of the FDA/CBER website:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf>

- Document includes information on submitting comments to Docket FDA-2013-D-0576

Conclusions

- OCTGT has published this draft guidance in hopes of facilitating early-phase clinical development of cellular and gene therapy products
- OCTGT is looking forward to receiving public comment and to discussions at the upcoming Advisory Committee in order to make the guidance as useful as possible

Acknowledgments

Rachael Anatol

Kim Benton

Peter Bross

Wilson Bryan

Kate Cook

Bindu George

Chanting Haudenschild

Ying Huang

Ilan Irony

Ke Liu

Richard McFarland

Skip Nelson

Melissa Reisman

Laura Rich

Michelle Roth-Klein

Bruce Schneider

Mercedes Serabian

Dan Takefman

Celia Witten

Rachel Witten

Keith Wonnacott

Lei Xu

OCTGT Contact Information

- John Hyde John.Hyde@fda.hhs.gov
- Regulatory Questions:
Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov or by calling (301) 827-6536
- OCTGT Learn Webinar Series:
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>



Public Access to CBER

CBER website:

<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)

Email: ocod@fda.hhs.gov

Phone: 301-827-3821

Manufacturers Assistance & Technical Training Branch (MATTB)

Email: industry.biologics@fda.gov

Phone: 301-827-4081

Follow us on Twitter

<https://www.twitter.com/fdacber>



Comments on the Guidance

Docket FDA-2013-D-0576

- Electronic comments: <http://www.regulations.gov>
- Written comments:
 Division of Dockets Management (HFA-305)
 Food and Drug Administration
 5630 Fishers Lane, Rm. 1061
 Rockville, MD 20852
- Questions:
 Office of Communications, Outreach and Development:
ocod@fda.hhs.gov, 1-800-835-4709, 301-827-1800, or
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>