Regulatory Updates for Human Gene Therapy Products: An FDA Perspective

CASSS Cell and Gene Therapy Workshop
Regulatory Updates from Across the Globe
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Human Gene Therapy 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 technology (e.g., gRNA, RNP, endonucleases)
  – Ex vivo genetically modified cells
GT Product Approvals by FDA

• Kymriah (Tisagenlecleucel)
  • CD19-directed genetically modified autologous T cell immunotherapy
  • For treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

• Yescarta (Axicabtagene Ciloleucel)
  • CD19-directed genetically modified autologous T cell immunotherapy
  • Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

• Luxturna (Voretigene Neparvovec)
  • Adeno-associated virus vector-based gene therapy
  • Indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.
INDs/IDEs Received per Calendar Year in OTAT

82 new GT IND (2018)
133 new CT IND (2018)
CAR T cell Targets

111 active CAR T cell investigations in OTAT as of 6/30/18

CD19:
- Expressed on B-cells
- Targets hematologic cancers
Human gene therapies involving genome editing technology

- ZFN
- TALEN
- CRISPR
- Other

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Guidance Documents Updates
• Tissues and Advanced Therapies: *Draft Guidance Documents CBER is Planning to Issue in 2018:*

  – Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); (GT CMC)
  – Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus during Product Manufacture and Patient Follow-up; (RCR guidance)
  – Observing Subjects Who Received Human Gene Therapy Products for Delayed Adverse Events; (LTFU)
  – Human Gene Therapies for Hemophilia

CBER Initiatives - Guidance Documents (2)

- Tissues and Advanced Therapies: *Draft Guidance Documents CBER Issued in July 2018:*

- Clinically focused guidance documents:
  - Human Gene Therapy for Hemophilia
    - Also considerations for laboratory tests for coagulation factors
  - Human Gene Therapy for Rare Diseases
  - Human Gene Therapy for Retinal Disorders

- Disease specific preclinical and CMC recommendations

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); (Draft, July 2018)

- Update recommendations based on FDA and ICH guidance documents and changes to regulations since 2008
- Update the list of terms and definitions
  - e.g., human gene therapy, human gene therapy product, genome editing
- Recommendations for providing CMC information into eCTD
  - Module 1: recommendations for administrative information
  - Module 2: summary information detailed in Module 3
  - Module 3: detailed instructions for CMC information to be submitted to support an IND
- Appendices:
  - Facility/equipment, quality unit, COAs, adventitious agents safety data

www.fda.gov
• Categorization of viral vectors for genetically modified cells
  – Critical manufacturing component, recorded in DS section of Module 3 to capture all necessary information
  – Manufactured under GMPs, process and method validation for licensure.

• Key updates to product and method development
  – Cell bank selection, impurity testing, and residual DNA testing
    • Quality controls and verification for CMO
  – Qualification of dose determining assays
  – Plasmids for further manufacture
  – Replication competent virus testing (see RCR guidance)
Expand the scope to cover all members of retroviridae family

Little change to vector testing requirements
  - Updated recommendations for amount of product to be tested
    • Sensitivity < 1 RCR / patient dose

Update testing recommendations for *ex vivo modified cells*:
  • All products to be tested (i.e., remove 4-day rule)
  • Rapid methods allowed for RCR lot release testing
  • RCR release testing may be discontinued if justified by manufacturing experience and vector design

Update to patient monitoring expectations

Add post-licensure considerations
• Update scope and background
  – Include lentiviral vectors, transposon-based vectors, and genome editing technologies
  – Experience gained through past LTFU studies
• Updates to preclinical evaluations to assess risk of GT products
• Clarification of recommendations for LTFU protocols for investigational GTP
  – e.g., collecting delayed adverse event data, protocol template, duration of LTFU
• Considerations for post-marketing monitoring plans for GTP
• LTFU in relation to post-licensure Registry and Risk Evaluation and Mitigation Strategy (REMS)
CMC Activities Related to Product Licensure

- Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products (Draft Guidance for Industry posted in December, 2017)
  —Review of public comments underway
- ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (Draft Guideline posted in November, 2017)
- Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products (Draft Guidance for Industry posted in May, 2015)
CBER Initiatives - Guidance Documents

• **Guidance Documents Issued since the July 2017 Guidance Agenda Update:**

  – Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry (issued November 2017)

  – Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry (November 2017)

  – Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff (November 2017; updated December 2017)

Thank you
CBER Contact Information

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• **Regulatory Questions:**
  Contact the Regulatory Management Staff in OTAT at CBEROCTGTRMS@fda.hhs.gov
  or Lori.Tull@fda.hhs.gov

• **References for the regulatory process for OTAT**

• **OTAT Learn Webinar Series:** [http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm](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

- Consumer Affairs Branch (CAB) Email: ocod@fda.hhs.gov

- Manufacturers Assistance and Technical Training Branch (MATTB) Email: industry.biologics@fda.gov

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