Regulatory Expectations for Cell and Gene Therapies

4th PQRI/FDA Conference on Advancing Product Quality: *Patient-Centric Product Design, Drug Development, and Manufacturing*

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Outline

• Introduction
• CMC expectations for early-stage product development
• CMC expectations for late-stage product development
• Accelerating product development - FDA initiatives
• Summary - Cautious Optimism in Gene Therapy
FDA Approved Oncolytic and GT Products

• Imlygic (Amgen- HSV- Approved 2015)
  – Genetically modified oncolytic viral therapy
  – for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

• Luxturna (Spark- AAV-GT Approved 2017)
  – For the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

• Kymriah (Novartis- Lentivirus- Approved 2017)
  – CD19-directed genetically modified autologous T cell immunotherapy
  – For up to 25 year old with acute lymphoblastic leukemia (ALL)

• Yescarta (Kite- Retrovirus- Approved 2017)
  – CD19-directed genetically modified autologous T cell immunotherapy
  – For adult patients with relapsed or refractory large B-cell lymphoma (DLBCL)
Rapid Growth in Annual GT IND Applications

- Imlygic, Sept 2015
- Yescarta, Oct 2017
- Luxturna, Dec 2017
- Kymriah, Aug 2017

* Projected based on 108 INDs received till April 2019
Gene Therapy Vectors

Rapid growth in AAV and Lentivirus as vectors of choice in GT

![Pie chart 2014]

- Other (4%)
- AAV (5%)
- Retrovirus (21%)
- Adenovirus (16%)
- Plasmid (31%)
- Bacteria (4%)
- Pox Virus (9%)
- HSV (2%)

![Pie chart 2018]

- Other (2%)
- AAV (12%)
- Retrovirus (17%)
- Adenovirus (14%)
- Lentivirus (17%)
- Plasmid (19%)
- Bacteria (5%)
- Pox Virus (9%)
- HSV (5%)
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

BCMA:
• B-cell maturation Antigen
• Expressed on malignant plasma cells

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**CMC Expectations: Progressive Refinement of Product Specifications**

- Early product characterization is a **multi-parameter** analysis
- Number of parameters progressively get pruned from phase I to phase III
- Major manufacturing changes during a pivotal trial should be avoided
- All changes need to be scientifically valid and justified
CMC Expectations for Early-Stage

Follow the Gene Therapy CMC guidance and test the Cells (MCB,WCB), Vector and the Drug product

- Develop assays to evaluate product Safety, Identity, Purity & Potency
- Set acceptance criteria
- Evaluate product stability
- Evaluate shipping conditions as appropriate
  - For AAVs, establish a robust product specific titer assay
  - For Lenti/Retroviral products, develop a potency assay for virus lot release
  - For Oncolytics, establish an assay to show that the manufacturing process does not alter the tropism or virulence
CMC Expectations for Early-Stage ..2

• Choice of cell substrate for vector manufacturing
  – Use of tumorigenic cells in vector manufacture may require additional tests

• Plasmid purity- evaluate the plasmids for other contaminating plasmids
  – Plasmids manufactured in a multi product manufacturing facility should be tested for other products made in the facility

• Reagents- Use FDA approved or cleared reagents
  – Use the highest grade reagents available
  – All reagents of animal and human origin must be tested for potential pathogens

• Follow cGMP requirements
  – At a minimum, follow the Phase 1 cGMP requirements
CMC Expectations for Early-Stage...

• Ensure that the pre-clinical and clinical study products are comparable
• Keep retained samples for future comparability studies
• Develop a quantitative assay to measure product potency
• All assays should be qualified (evaluated for sensitivity and specificity*)
• Ensure reagent supply to at least last the study duration

* May require evaluation of additional parameters depending on the product

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Product characterization increases with phase of clinical investigation

Expected compliance with all applicable regulations:

- **Development**: Focus largely on product safety issues
- **Preclinical**: Focus largely on product safety issues
- **Phase I**: Increasing expectations for product characterization & compliance with cGMPs
- **Phase II**: Increasing expectations for assuring product quality and consistency of manufacturing
- **Phase III**: Full compliance required for licensure
- **BLA**: Full compliance required for licensure

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CMC Expectations for Late-Stage Product Development

• Have sufficient manufacturing experience to narrow acceptance limits

• Have a controlled manufacturing process
  - Sufficient knowledge of the manufacturing process to determine Critical Process Parameters (CPP)
  - Sufficient knowledge to set in-process quality criteria: set Action Limits and Rejection Limits
  - Sufficient knowledge to plan for future production scale up

• Have assays well developed and nearly completely validated

• Have a biologically relevant potency assay
  - An assay capable of measuring the product’s biological activity

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Opportunities for Interaction with FDA

Development
Preclinical
Phase I
Phase II
Phase III
Marketing

Clinical Trials

IND Submitted
Interactions related to BT/RMAT designations
BLA Submitted

PreIND Meeting
End of Ph 2 Meeting
PreBLA Meeting

INTERACT

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• **Accelerating product development: FDA’s initiatives**

• Summary - Cautious Optimism in Gene Therapy
Accelerating Product Development

• Explore the various accelerated product development pathways offered by FDA
  – Fast Track (FT)
  – Breakthrough (BT)
  – Regenerative Medicine Advanced Therapy (RMAT)
  – Accelerated Approval
  – Priority Review

• Engagement with FDA
  – Initiate dialogue with the Agency
  – Discuss development milestones
Accelerating Product Development CBER Initiatives

Facilitating additional Interactions with FDA

- INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER products)

- RMAT (Regenerative Medicines Advanced Therapy)
Accelerating Product Development: CBER Initiatives

GT guidance documents in 2018:

1) Three Disease specific Guidance documents:
   – Treatment of hemophilia
   – Treatment of Retinal Disorders
   – Treatment of Rare Diseases

4) CMC guidance for GT products

5) Testing for Replication competent retrovirus (RCR)

6) Long term follow-up
Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (DRAFT, July 2018)
Draft CMC Guidance

• 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
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.
  - Manufacturer may be inspected during BLA review

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)
Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

Draft Guidance for Industry (July 2018)
Updates in RCR Guidance

• Revised recommendations for testing working cell banks for retroviral producer cells
• Revised recommendation for the amount of retroviral vector to be tested
  – ensure <1 RCR per dose (revised from quantity made)
Updates in RCR Guidance (2)

• Updated testing recommendations for ex vivo modified cells:
  • All products should 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 data from manufacturing experience and vector design

• Updated patient monitoring expectations

• Added post-licensure considerations
Long Term Follow-up After Administration of Human Gene Therapy Products

Draft Guidance for Industry
(July 2018)
Updates in LTFU Guidance

• Updates to 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
• Clarified recommendations for LTFU protocols for investigational GTP
  – e.g., collecting delayed adverse event data, protocol template, duration of LTFU
• Added considerations for post-marketing monitoring plans
  – LTFU in relation to post-licensure Registry and Risk Evaluation and Mitigation Strategy (REMS)
Summary

- Gene therapy has the potential to cure diseases and conditions that have been incurable
- With the approval of the initial few GT products, there is high expectation of future application of GT
- As our knowledge of the biology of GT vectors and diseases grow we expect to have safer GT products
- Vigilance is essential and we do not want to forget the lessons learned from past collective clinical experiences with GT products
Optimistic Outlook for Gene Therapy

“... There is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable — or that the field still requires special oversight that falls outside our existing framework for ensuring safety”

- Francis S. Collins, M.D., Ph.D., and Scott Gottlieb, M.D.

August 15, 2018,
The NEW ENGLAND JOURNAL of MEDICINE
Contact Information and Resources

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Cell and Gene Therapy Guidance documents:
https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceandregulatoryinformation/guidances/cellularandgenetherapy/default.htm

OTAT Learn Webinar Series:
http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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