US FDA Initiatives: Promoting and Protecting the Public Health While Supporting Innovation

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Regulating Innovative Therapies: A Balancing Act

Experience and Programs in FDA’s Center for Biologics Evaluation and Research
Outline

- Regulatory Philosophy
- Historical Perspective: Gene Therapy
  - X-SCID case study
- What is FDA doing now to foster innovation?
Regulatory Philosophy: Protect Public Health; Promote Innovation

*(more on these themes later)*

- Collaborative
- Fund intramural and extramural applied research to address gaps in scientific knowledge and methods to assess regulated products *(Regulatory Science)*
- Outreach
- Guidance Documents
- Provide opportunities for FDA advice throughout product development
- Lifecycle approach (discovery through post-market)
Gene Therapy Evolution

CASE STUDY: X-LINKED SEVERE COMBINED IMMUNODEFICIENCY
Gene Therapy Raises Unique Regulatory Concerns

• Certain Viral Vectors: potential for rescue of replicating virus
• Potential for unintended permanent alteration to somatic or germline DNA
  – Long-term toxicity
  – Risk of secondary cancer
• Potential for inappropriate immune response to vector components or transgene
Early Milestones of Gene Therapy

• 1990 – first clinical trial
  Retroviral vector-mediated gene transfer into T cells to treat ADA-SCID

Dr. Anderson's Gene Machine
By Robin Marantz Henig
March 31, 1991
## Notable Early Milestones

### Other Vectors
- 1992, Plasmid for alpha-1 anti-trypsin deficiency
- 1993, Adenovirus Vector for Cystic Fibrosis
- 1995, Adeno-associated vector for Cystic Fibrosis
- 2002, Lentivirus vector for HIV-1

### Successes
- 2000, Successful treatment of X-SCID with retroviral vector-mediated gene transfer via hematopoietic stem cells (France)
- 2004, First licensed gene therapy, China, Adenovirus vector for cancer

### Problems
- 1999, Jesse Gelsinger dies in adenovirus vector clinical trial for ornithine transcarbamylase deficiency
- 2002, Two leukemias reported in children in retroviral vector-mediated gene transfer via hematopoietic stem cells in clinical trial for X-SCID (France)
Case Study on Regulation and Innovation
Gene Therapy Clinical Trial in X-SCID Patients

Gene Therapy Approach

Isolate CD34+ HSC

Expand in Flt3L, SCF, MDGF, and IL-3

Expose to Retroviral Vector Encoding Common gamma chain

Reinfuse Into patient
Insertional Tumorigenesis and Retroviral Vectors

*Early Assumptions*

- Wildtype Retroviruses
  - Tumorigenesis
  - Genetic aberrations
- Acknowledged risk in use of retroviral vector-mediated gene therapy
  - In absence of replication, finite number of sites for genomic integration (reduced risk)
  - Greatest risk perceived with Replication-Competent Retrovirus (RCR)
Insertional Tumorigenesis and RCR

- RCR may arise from recombinational events in retroviral vector-producing cells during production
- 1992: Immune suppressed monkeys exposed to bone marrow cells transduced with a preparation of RCR-positive retroviral vector
  - 3/10 developed lymphomas, died within 200 days
  - Monkeys had sequences identified as recombinants between vector and helper or between vector and endogenous sequences.

Regulatory guidance focused on risks associated with RCR recommending rigorous testing throughout vector production

X-SCID: What happened?

- Out of total of 20 children with X-SCID treated (France and UK clinical trials)
  - France:
    - 10/11, Clinical and laboratory evidence of engraftment and benefit early\(^1\)
    - 8 patients alive at median 9 years follow-up; 7 with sustained immune reconstitution\(^3\)
  - 5/20 children with engraftment developed leukemia\(^2, 3, 4\)

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X-SCID Gene Therapy

Increased Transduction Rates

In vivo Selective Advantage; Disease Factors

THERAPEUTIC BENEFIT

INCREASED RISK

<table>
<thead>
<tr>
<th>Discussions at Advisory Committee</th>
<th>Implement long-term follow-up: gene therapy clinical trials</th>
<th>Workshop on long-term follow-up, 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov, 2000</td>
<td>2001, implemented for all clinical trials</td>
<td>Issued Draft Guidance, 2005, for comments</td>
</tr>
<tr>
<td>April, 2001</td>
<td>Retroviral vector trials also needed to perform additional monitoring for clonality of vector integration</td>
<td>Revised based on comments</td>
</tr>
<tr>
<td>October, 2001</td>
<td></td>
<td>2007, Issued Final Guidance: Gene therapy clinical trials – observing participants for delayed adverse events</td>
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</table>
Fast Forward
Gene Therapy Milestones Today

**October, 2017**
- Kymriah, Novartis Pharmaceuticals Corporation
- Approved for acute lymphoblastic leukemia
- CD19-directed Chimeric Antigen Receptor (CAR) T-cells (autologous)

**December, 2017**
- Luxturna, Spark Therapeutics, Inc.
- Approved for treatment of patients with biallelic RPE65 mutation-associated retinal dystrophy
- Adeno-associated virus vector expressing RPE65

**May, 2018**
- Yescarta, Kite Pharma, Incorporated
- Approved for B cell lymphoma
- CD19-directed CAR T-cells (autologous)

**May, 2019**
- Zolgensma, AveXis, Inc
- Approved for pediatric patients less than 2 year with spinal muscular atrophy
- Adeno-associated virus vector expressing SMN1 gene
Fostering Innovation Now and Into the Future:

WHAT ARE WE DOING NOW?
Regulatory Philosophy: Protect Public Health; Promote Innovation

- Collaborative
- Fund intramural and extramural applied research to address gaps in scientific knowledge and methods to assess regulated products (aka Regulatory Science)
- Outreach
- Guidance Documents
- Provide opportunities for FDA advice throughout product development
- Lifecycle approach (discovery through post-market)
Collaborative Approach to the Regulation of Biologics

Review of Data Submitted to FDA
Active Research
Surveillance
Internal CBER Discussion
External Experts

CBER researcher = “Researcher-Reviewer”

The integration of research and review
• ensures relevance, expertise, timeliness, and usability
• fosters rational policy and decisions based on sound science, law and public health impact
Development of new or evaluation of existing non-clinical models.

Methods development and evaluation of products for safety, potency, purity, stability, and clinical effectiveness.

Biomarker development and evaluation

Development of reference materials to support product quality and consistency

Methods Development to Support Seasonal and Pandemic Influenza Activities
TCPro: an In Silico Risk Assessment Tool for Biotherapeutic Protein Immunogenicity

What was done?
A computational tool that predicts the immune response of CD4+ T cells to specific biotherapeutic drugs. TCPro emulates standard *ex vivo* T cell assays.

What was learned?
Immune reaction risk of 15 licensed protein-based products predicted using TCPro is consistent with the actual reported clinical experience with these biotherapeutics.

Why is this important?
Biotherapeutic proteins may induce anti-drug antibodies. TCPro provides a new tool for rapid, initial screenings of new biologics in early stage development.
New Programs and Legislative Authorities
Supporting Regulatory Processes
Fostering Innovation

• Early Engagement
• Outreach and Engagement
• PDUFA VI Commitments
• 21st Century Cures
Added Program for Early Engagement

INTERACT: INitial Targeted Engagement for Regulatory Advice on CBER products (previously known as pre-pre-IND interactions)

INTERACT
Pre-IND meetings
Outreach and Engagement

• Informative talks at relevant meetings
• Public workshops to engage stakeholders
• Participation in Public Private Partnerships
• Webinars, for example, OTAT Learn, 22 topics: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
• Guidance Documents
PDUFA VI Commitments:

- Model-informed Drug Development
- Complex Innovative Designs (21st C Cures also)
- Drug Development Qualification Program (21st C Cures also)
PDUFA VI: Advancing Model-Informed Drug Development (MIDD)

- Develop Regulatory Science and Review Capacity
- Conduct Series of Workshops
- Publish Guidance, MAPPs, or SOPPs
- Conduct Pilot Meeting Program

MIDD Pilot Meeting Program*

• Fulfills a performance goal agreed to PDUFA VI

• CBER & CDER accept 2-4 paired-meeting request quarterly each year throughout PDUFA VI period (April, 2018 to June, 2022)

• MIDD Pilot Program is designed to provide:
  - Opportunity for sponsor and FDA to discuss the application of MIDD approaches to the development & regulatory decision
  - Advice about particular MIDD approaches addressing specific drug development program

*RESOURCES:
Federal Register
Website:

For more information, contact FDA at MIDD@FDA.HHS.GOV
Drug/Biologic Company with Active IND or PIND can Apply for the MIDD Pilot; Initial Priority Areas:

**Dose selection/estimation**
- e.g. identify covariate to inform dosing regimen, estimate exposure-response, etc.

**Clinical trial simulation**
- e.g. drug-trial-disease models to inform duration of trial, select response measure, pediatric trial design, etc.

**Predictive or mechanistic safety evaluation**
- e.g. use of systems pharmacology models for predicting safety or identifying biomarkers, etc.
PDUFA VI: Enhancing Capacity to Review Complex Innovative Designs

- CID roughly defined: designs for which trial simulations are needed to establish operating characteristics

- Commitments/Accomplishments:
  - Develop staff capacity to review CID
  - Start a pilot program for highly innovative trial designs
    - FR Notice, several applications received
    - Results will be published: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm617212.htm
  - Public workshop to discuss CID (held, 3/20/18)
  - Draft guidance on complex adaptive designs (published 9/2018)
  - Develop or revise relevant MAPPs, SOPPs, etc. for review of CID that rely on trial simulations
PDUFA VI: Drug Development Qualification Program

• Drug Development Tools include:
  – Animal Studies
  – Clinical Outcomes Assessments
  – Biomarkers

• 21st C. Cures DDT Qualification
  – 3-step submission process: letter of intent; qualification plan; full qualification package
    • https://www.fda.gov/AboutFDA/Innovation/ucm512503.htm
  – FDA accept/not accept
RESOURCES

BEST: BIOMARKERS, ENDPOINTS, & OTHER TOOLS

• A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
  
  https://www.fda.gov/AboutFDA/Innovation/ucm512503.htm

• Created by the NIH-FDA Biomarker Working Group, including CBER representatives

• Publicly available at
  

CDER BQP website — procedures, policies, prior submissions & FDA letters, qualified biomarkers
21st Century Cures

- Advanced Manufacturing Initiative
- Addition of Regenerative Medicine Advanced Therapy to Suite of Expedited Programs
- Standards Development
21st C Cures: Added RMAT to Expedited Programs

- **Accelerated Approval Regulations: 1992**
  Section 506(c) of Food, Drug & Cosmetic Act (FD&C Act)

- **Priority Review Designation: 1992**
  Prescription Drug User Fee Act

- **Fast Track Designation (FTD): 1997**
  Section 506(b) of FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act

- **Breakthrough Therapy Designation (BTD): 2012**
  Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act

- **Regenerative Medicine Advanced Therapy (RMAT): 2016**
  Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act
FDA Expedited Programs: Guidance Documents

Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (2014)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions
21st C Cures: Emphasis and Resources to support Advanced Manufacturing

• Why advanced manufacturing? Products may require complex manufacturing processes, advanced manufacturing may bring new tools to address:
  – Flexibility
  – Availability
  – Scalability
  – Cost

• What do we mean by advanced manufacturing? Innovative technologies that could include:
  – Cell culture systems supporting large scale or rapid production
  – Enabling tools such as measurement technology
CBER Initiatives to Promote Development of Advanced Manufacturing Technologies

The CBER Advanced Technology Team (CATT)

- Interactive mechanism to prospective developers to discuss the implementation of new technologies supporting development of CBER-regulated biologics products
- Access to early interactions on more general topics before filing of a regulatory submission

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

Build internal scientific and regulatory expertise

- Develop and support CBER research programs to improve understanding of advanced manufacturing for vaccines and cell and gene-based therapies

Promote the creation of more modern Domestic Manufacturing

- CBER awarded several grants and contracts to foster advanced manufacturing of biological products
- Goals of funded projects
  - Addressing knowledge and experience gaps identified for emerging manufacturing and testing technologies
  - Support the development and adoption of such technologies in the biological product sector
21st C Cures: Promoting Standards Activities

• 21st Century Cures Act, 2016
  – Section 3036 development of standards for regenerative medicine therapies, including products designated regenerative medicine advanced therapies. In consultation with the National Institute of Standards and Technology (NIST) and stakeholders, FDA is facilitating efforts to coordinate the development of standards for regenerative medicine therapies.

Gammaretroviral-Mediated Endogenous Gene Activation

Psi (Internal Promotor) Transgene

Gene Disruption

Read-through Transcription

Distal Gene Activation

Dysregulated Gene Expression

Tumorigenesis
## Comparison of Expedited Programs Criteria

<table>
<thead>
<tr>
<th><strong>Fast Track</strong></th>
<th><strong>Breakthrough Therapy</strong></th>
<th><strong>RMAT</strong></th>
<th><strong>Accelerated Approval</strong></th>
<th><strong>Priority Review</strong></th>
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<tr>
<td>-Serious condition AND</td>
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<td>-Nonclinical or clinical data demonstrate the potential to address unmet medical need</td>
<td>-Preliminary clinical evidence indicates that the drug may demonstrate <strong>substantial improvement over available therapy</strong> on one or more clinically significant endpoints</td>
<td>-It is a regenerative medicine therapy - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition</td>
<td>- Meaningful advantage over available therapies - Demonstrates an <strong>effect on</strong> either: a <strong>surrogate endpoint or an intermediate clinical endpoint</strong></td>
<td>-Demonstrates potential to be a significant improvement in safety or effectiveness</td>
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Note: Information to demonstrate potential depends upon stage of development at which FT is requested.

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<td>Serious condition AND Nonclinical or clinical data demonstrate the potential to address unmet medical need</td>
<td>Serious condition AND Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints</td>
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1. FDA Guidance for Industry: Expedited Programs for Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
2. FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, February, 2019
## Comparison of Expedited Programs Features

<table>
<thead>
<tr>
<th>Accelerated Approval</th>
<th>Priority Review</th>
<th>Fast Track (FT)</th>
<th>Breakthrough Therapy (BT)</th>
<th>RMAT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval based on surrogate or intermediate clinical endpoints</td>
<td>Shortened Review Clock</td>
<td>Frequent meetings</td>
<td>All FT Features, including:</td>
<td>All FT and BT Features, including early interactions to discuss any potential surrogate or intermediate endpoints</td>
</tr>
<tr>
<td>Save valuable time in the drug approval process</td>
<td>FDA will take action on an application within 6 months (compared to 10 months under traditional review)</td>
<td>Eligibility for *:</td>
<td>Actions to expedite development and review; Rolling review + Intensive guidance on an efficient drug development program</td>
<td>+ Statute addresses potential ways to support accelerated approval</td>
</tr>
<tr>
<td>Reduce waiting period for patients to obtain clinically meaningful benefit.</td>
<td></td>
<td>✓ Priority Review ✓ Rolling Review</td>
<td>Organizational commitment involving senior managers</td>
<td></td>
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*if relevant criteria are met

1. FDA Guidance for Industry: Expedited Programs for Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
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