

# FDA's Role in Expediting the Development of Novel Medical Products

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June 13, 2019



# Topics Covered

- Brief history of FDA
- Expediting product development
- Expedited programs for development
- Hypothetical product example



# How a Regulatory Agency Comes into Existence

- 1901 13 children in St. Louis, MO die of tetanus after receiving contaminated diphtheria antitoxin and 9 children in Camden, NJ die after receiving contaminated smallpox vaccine
  
- 1902 Biologics Control Act passed requiring the licensing of manufacturers of vaccines, serums, and antitoxins, as well as authorizing the inspection of manufacturing facilities

# FDA's History

- 1902      Biologics Control Act
- 1906      Food and Drugs Act
- 1938      Federal Food, Drug and Cosmetic Act
- 1944      Public Health Service Act
- 1962      Kefauver-Harris Amendments
- 1976      Medical Device Amendments
- 1992      Prescription Drug User Fee Act

# Regulatory Framework

- Constitution
- Laws/Statutes
  - Public Health Service Act
    - Section 351
    - Section 361
  - Federal Food Drug and Cosmetic Act
- Regulations/Rules
- Guidance



# Promoting Product Development

- An increasingly important part of FDA's mission is to facilitate the development and approval of innovative products that address unmet medical needs
  - User Fee Acts (PDUFA, MDUFA, BsUFA, GDUFA)
  - Orphan Designation
  - Priority Review Vouchers
  - Expedited Development Programs

# User Fee Acts

- In return for the fees charged to sponsors, the Prescription Drug User Fee Act (PDUFA) placed performance metrics on FDA and established programs facilitating the development of certain drugs and certain biologics
- The first five-year PDUFA program was enacted in 1992, now on PDUFA VI
  - MDUFA IV, BsUFA II, GDUFA II

# Orphan Product

## Designation and/or Exclusivity

- To qualify
  - Drug or biologic intended for safe and effective treatment, diagnosis or prevention of rare diseases affecting less than 200,000 people in the U.S. or if affecting more people, cost recovery is not expected from marketing a treatment drug
- Features
  - Tax credits for qualified clinical testing
  - Exempt from prescription drug user fee
  - If approved, 7 years of marketing exclusivity





# Priority Review Voucher Programs

- Neglected Tropical Disease
- Rare Pediatric Disease
- Medical Countermeasure



# Expedited Development Programs

- Fast Track
- Priority Review
- Accelerated Approval
- Breakthrough Therapy
- Regenerative Medicine Advanced Therapy

These programs may be applicable to drugs or biologics intended to treat serious conditions

# Fast Track

**For drugs or biologics intended to treat serious conditions**

- To qualify
  - Nonclinical or clinical data demonstrate potential to address unmet medical need **OR** drug has been designated a qualified infectious disease product
- Features
  - Actions to expedite development and review
  - Rolling review

# Priority Review

**For drugs or biologics intended to treat serious conditions**

- To qualify
  - Approval would represent significant improvement in safety or effectiveness **OR** pediatric study report supplement **OR** application for drug designated as qualified infectious disease product **OR** application submitted with a priority review voucher
- Features
  - Shorter clock for review of marketing application (6 month compared with 10 month standard review)

# Accelerated Approval

**For drugs or biologics intended to treat serious conditions**

- To qualify
  - Drug or biologic provides a meaningful advantage over available therapies **AND** demonstrates an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit
- Features
  - Approval based on effect on a surrogate endpoint
  - Confirmatory trial(s) are required to verify the clinical benefit or effect on irreversible morbidity or mortality

# Breakthrough Therapy

**For drugs or biologics intended to treat serious conditions**

- To qualify
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint or endpoints over available therapies
- Features
  - Intensive guidance on efficient drug development
  - Organizational commitment
  - Other actions to expedite review (e.g., rolling review)

# Regenerative Medicine Advanced Therapy Designation (RMAT)



- To expedite the development and review of regenerative medicine advanced therapies
  - Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
  - Genetically modified cell therapies and gene therapies producing durable effects included

# Regenerative Medicine Advanced Therapy Designation (RMAT)



- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designated products are eligible as appropriate for priority review and accelerated approval
- Post-approval requirements can be fulfilled by
  - Clinical studies, patient registries or other sources of real world evidence such as electronic health records; collection of larger confirmatory datasets; post-approval monitoring of all patients treated





# FDA and Product Development

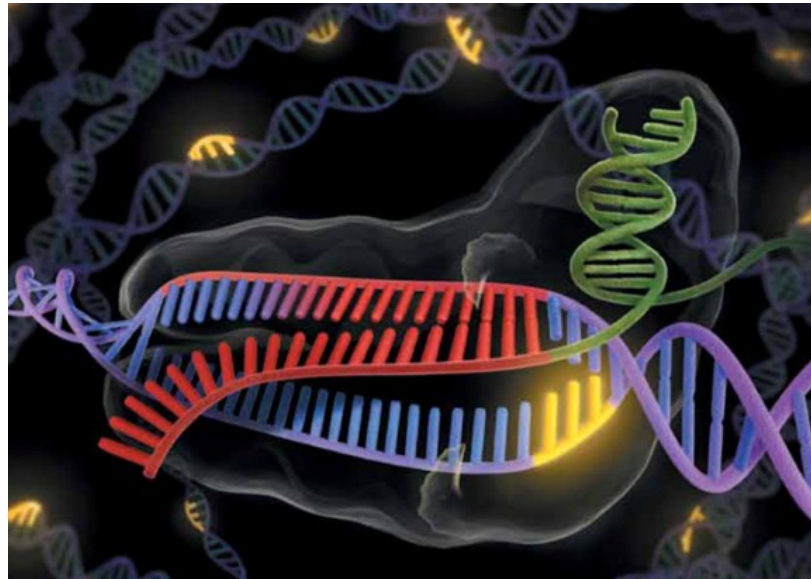
- FDA is responsible for ensuring that medical products are safe and that they meet a standard for efficacy
- A number of different expedited programs exist to facilitate product development particularly for serious medical conditions

# Developing a Novel Therapy

Taking an investigational agent  
through development to become  
a marketed product

The following product is fictional and for instructional purposes only –  
any resemblance to an actual product in development is purely coincidental

# Hypothetical Product Example: CRISPR-Cas9 Gene Therapy to Treat a Rare Bleeding Disorder Caused by a Missense Mutation



# Factor V Deficiency (Parahemophilia)

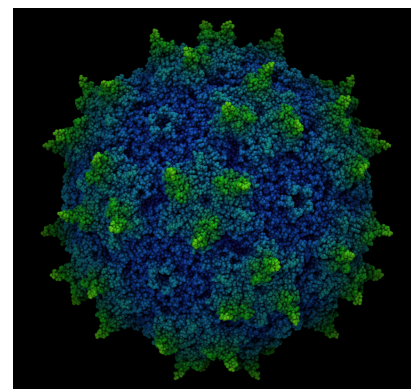
- Factor V is the precursor to factor Va, an cofactor needed for normal blood clotting to occur
  - ~330 kD glycoprotein made in the liver
  - Taken up by megakaryocytes through endocytosis so that it is present in platelets
- Rare clotting factor deficiency, 1:500,000
- A number of mutations have been described
  - Nonsense, missense, deletions
- Manifestations vary from mild to severe bleeding

# Genome Editing Technology

- DNA is inserted, deleted, or replaced in the genome of an organism using engineered nucleases, or “molecular scissors”
- Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 system is one of several genome editing tools
- Single base pair editing is now potentially possible using a modified CRISPR-Cas9 fused to a cytidine deaminase enzyme
  - Converts cytidine to uridine (C→T or G→A)

# Therapeutic Concept

- Desire to correct severe bleeding phenotype in individuals with a missense mutation at T1927C (C585R, cysteine to arginine)
- Use a modified CRISPR-Cas9 fused to a cytidine deaminase targeted to the site of the mutation expressed in an AAV8 vector



# Sponsor-FDA Interaction

- A request for an informational meeting regarding the investigational new drug (IND) application submission process is made to help understand the process and to discuss questions about studies that would need to be conducted prior to first in human trials
  - This type of meeting is called a pre-pre-IND or INTERACT meeting

# Sponsor-FDA Interaction

- At the meeting several preclinical studies are recommended
- The suggestion is made to evaluate the on and off target effects of the construct in a human hepatocyte organ on a chip model that is commercially available
- The agency also notes that an environmental assessment will be needed since a viral construct is being administered



# Regulatory Guidance

- The Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) also refers to two relevant documents that may provide answers to a number of questions

**Considerations for the Design of  
Early-Phase Clinical Trials of  
Cellular and Gene Therapy Products**

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**Guidance for Industry**

**Guidance for Industry**

**Preclinical Assessment of  
Investigational Cellular and Gene  
Therapy Products**

# Preclinical Development

- Experiments are conducted using the construct in the human hepatocyte system and indicate that targeting is highly specific with undetectable targeting of other sites by Indel (insertion deletion) analysis
- A proposed manufacturing process is developed for the vector that is in keeping with Good Manufacturing Practices (GMP)

# Sponsor-FDA Interaction

- Having assembled the available data and having drafted a Phase 1 protocol concept , a pre-IND meeting request is submitted to FDA
- The meeting package includes questions, to the appropriate office at FDA (OTAT) and is sent at least 4 weeks in advance of the meeting, which is scheduled within 60 days
- FDA provides a written response and a mutual decision is made to cancel the meeting

# Regulatory Submission

- Following some additional scientific work to address FDA issues and drafting of a complete Phase 1 protocol the IND package is submitted
- Within 30 days a letter is received indicating that the clinical trial may proceed
  - The alternative would have been to receive a telephone call within 30 days from FDA placing the study on clinical hold

# Phase 1/2

- The protocol involves the treatment of 6 individuals with the T1927C mutation
  - Single dose is chosen based on prior experience with vector and small number of available subjects
- The vector is to be administered once intravenously and the patients will initially be monitored for six months with measurement of factor V levels
- A variety of safety parameters will also be monitored (e.g., liver function tests) and long term safety follow up is planned

# Phase 1

- Results from the Phase 1 study
  - Factor V levels
    - Pre: <1%
    - Post: 35%
  - Bleeding episodes requiring plasma infusion
    - Over 6 months prior to enrollment: median 3 per subject
    - During 6 months after enrollment: none observed

# Sponsor-FDA Interaction

- Believing that the data indicate the potential to address an unmet medical need, the sponsor submits a request for regenerative medicine advanced therapy (RMAT) designation to FDA
- After reviewing the information submitted, RMAT designation is granted by FDA
- Initial interactions following the designation focus on manufacturing and endpoints for proceeding with further clinical trials

# Further Development

- Given the small patient population, it is agreed that data from a trial in which 16/20 (80%) of treated patients achieve factor V levels >30% for at least 6 months could support accelerated approval
- Using the RMAT provisions it is agreed that following those 20 patients for 2 years and demonstrating continued benefit would provide confirmatory data for full approval



# Sponsor-FDA Interaction

- Following the enrollment of the 20 subjects and completion of 6 months of follow-up demonstrating that 18/20 (90%) of patients have levels of >30%, a pre-biologics license application submission meeting is held
- FDA and the sponsor agree on the nature of the manufacturing information, data tables and other content to be submitted in the application

# Application Submission Process

- With the RMAT designation, the submission is accepted in a rolling fashion (e.g., as individual sections are ready, they can be submitted)
- The submission receives priority review status
  - As part of the process there is interactive exchange including less formal interactions and a mid-cycle meeting and a late-cycle meeting

# Regulatory Considerations

- Safety considerations
  - Percentage of cleavage at on- and off-target sites
  - Identification and characterization of any off-target events in cells/tissues, including chromosomal translocations
  - Evaluation of the profile of insertions and deletions and types of mutations generated
- Benefit-risk analysis

# Advisory Committee Meeting

- An advisory committee consisting of experts in hematology and gene therapies is held to hear presentations from the company sponsor and the FDA on the trial results
- The advisory committee unanimously agrees that the product appears to be safe and effective for its intended use, but also raises concerns about long term risks from off target effects of gene editing that may have gone undetected with the Indel analysis performed

# Post-Marketing Requirements

- The company sponsor and FDA agree upon the nature of a post-marketing requirement for a safety study
  - All enrolled patients will be followed for 15 years to evaluate for the development of malignancy
  - All patients treated with the therapy will also be offered enrollment into a follow-up safety registry

**An approval letter is issued**

# Take Home Messages

- The next decades will see the development of numerous innovative medical products
- Regulatory approaches will need to either be developed or adapted to accommodate the novel nature of some of these entities
- FDA takes a scientific approach to regulation
- As FDA considers innovative technologies it must balance benefits against risks, taking into account uncertainties that exist

