FDA’s Role in Expediting the Development of Novel Medical Products

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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

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