

Special Considerations for Rare Diseases: OBRR Perspective

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Overview

- FDA Approval Standard for Drugs
- Challenges: FDA and Industry
- Regulatory Approval Mechanisms in US
- Clinical Trial Considerations for Rare Diseases
- Activities to Facilitate Licensure
- Examples of Products Recently Approved by the FDA for Rare Blood Disorders
- Summary

Approval Standard for all Drugs

- Substantial evidence of effectiveness
505(d) of the FD&C Act
- Demonstration of Safety
- Adequate quality control

Drug Approval: Benefit/Risk Balance

- FDA approval is based on the finding that the benefits of a drug outweighs the risk (known and potential) for a defined population for a specified indication(s).
- Benefit/risk findings occur on a “sliding scale” considering:
 - Severity of the disease
 - Availability of alternative treatments
 - Magnitude of the treatment benefit
 - Nature and frequency of serious adverse events

Challenges in Development of Products for Rare Diseases: Regulators Perspective

- Quantity of evidence available premarketing to support effectiveness and safety from “adequate and well controlled” studies are limited:
 - by small sample size
 - Estimates of safety and efficacy may have wide variability
 - Natural history not well understood

Challenges: Industry perspective

- Cost of research and clinical trials
- Limited market
- Regulatory burden

Regulatory Mechanisms for Approval in US

- Accelerated approval
 - Based on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit -----.”
- Priority review: 6 month review clock
 - Life and limb threatening conditions
 - Unmet medical need
- Animal rule:
 - Where clinical studies are both unethical and unfeasible

Overcoming Challenges of Study Designs for Rare Diseases

- Historical controls:
 - Natural history disease is well characterized and understood
 - Provisions are made for obtaining additional safety database (often through post-marketing registries)
- Crossover trials:
 - There is an alternative effective treatment
 - Short-term treatment with placebo is ethically acceptable

Overcoming (contd.)

- Adaptive trials
 - Ongoing adjustments to treatment regimen, dosing, participant allocation and /or sample size
- Sequential trials
 - Early stopping for strong negative or positive cumulative information

Activities Undertaken by OBRR to Facilitate Licensure

- Public discussion of evidence that could support licensure of orphan products
 - BPAC
 - varicella zoster immunoglobulin
 - Potential licensure pathway(s) for Coral snake antivenom
 - Guidance: Immunoglobulin
- Workshop:
 - Rare Plasma Protein Disorder workshop held in 2005
 - Alpha One Protease Inhibitor workshop 2009

Activities to Facilitate Licensure (contd.)

- Serve as liaison to groups such as North American Rare disorder working group, American Thrombosis Hemostasis Network (ATHN) and Center for Disease Control (CDC) to help them in developing registries, data gathering instruments etc.
- Encourage international collaboration

Example of Products Recently Approved Using Small-Scale Clinical Trial

- Ceprocin: Protein C Concentrate, (human), approved March, 2007
 - Approval process: priority review
 - Indication: severe congenital Protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans (PF)
 - Approval based on data from an open label, non-randomized, historically controlled study in 18 subjects
 - Additional safety data collected post-marketing via a registry

Examples (contd.)

- RiaSTAP: Fibrinogen Concentrate (Human), approved January 2009
 - Approval process: accelerated approval with priority review of the marketing application
 - Indication: treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia (incidence~1per million)
 - Approval based on data from pharmacokinetics and surrogate efficacy endpoint (Maximum Clot Firmness) in 15 subjects with afibrinogenemia.
 - Phase IV study to evaluate clinical efficacy and its correlation with surrogate endpoint is ongoing.

Examples (contd.)

- ATryn: recombinant ATIII produced from genetically engineered goats
 - Approval process: priority review
 - Indication: for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients
 - Approval based on data from two efficacy studies (N=35) compared to historical data for patients treated with plasma derived ATIII
 - Additional safety data being obtained via a post-marketing registry

Summary

- No compromise with scientific and regulatory standards
- Unmet medical need
- Encourage and work with sponsors to develop drugs and biologics for rare disease
- Innovative ways to demonstrate the safety and efficacy of these products
 - Development of novel clinical trial protocols that are appropriate for the size, nature and availability of existing treatments for the patient population
- Encourage international cooperation in product development