Don’t Do Different Things... *Do Things Differently!*
Drug Development in Rare Diseases

**Regulatory Perspectives on the Approval of Drugs for Rare Diseases**

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Disclaimer: The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the US Food and Drug Administration.
Outline

• Drug Development and Orphan Drugs/Rare Diseases in the United States: An Overview

• 1983 Orphan Drugs/Rare Disease Development – PROBLEM SOLVED?

• Challenges And the Role of the FDA-Science, Regulation, and Policy

• Quo Vadis?–Do Things Differently
DRUG DEVELOPMENT AND ORPHAN DRUGS/RARE DISEASES IN THE UNITED STATES: AN OVERVIEW
Chronology of Drug Development for Classical and Orphan Drug
Trends in Drug Discovery

An unsustainable trend for an Orphan Drug

Pre Orphan Drug Act: 1982

- 1973-1982: 10 new drugs for rare diseases
  - Little economic incentive for large pharmaceutical companies to pursue rare disease indications

- ≈7,000 rare diseases; 25 million people
  - In comparison: 67 million American adults (31%) have high blood pressure—that’s 1 in every 3 people in this room
    (http://www.cdc.gov/bloodpressure/facts.htm)

- ~85% of orphan diseases have a genetic basis
- Increasing by ~100 diseases/year
The Orphan Drug Act
21 CFR314.105
1983 ORPHAN DRUGS/RARE DISEASE DEVELOPMENT – PROBLEM SOLVED?
How Well Are We Doing?

- In past few years
  - ~1/3 of all NME approvals are Orphan products
  - 2/3 of therapeutic biological product approvals
- While there has been progress in the general science and approval of Orphan Drugs....just like an iceberg much more lies below the surface to be done.
  - 7,000 plus indications
- Since 1983
  - 3575 drugs with an orphan designation
  - 522 drugs approved........
Orphan Designations vs TOTAL Orphan Approvals*

*Includes Orphan Indications for Approved Drugs (re-purposing)
NME/NDA Approvals: Total vs Orphan

<table>
<thead>
<tr>
<th>Year</th>
<th>Total NME</th>
<th>Orphan NME</th>
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<tbody>
<tr>
<td>2010</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>2011</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>2012</td>
<td>33</td>
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<td>25</td>
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<td>30</td>
<td>10</td>
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<tr>
<td>2015</td>
<td>33</td>
<td>12</td>
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NME-BLA Approvals: Total vs Orphan

![Bar chart showing NME-BLA approvals from 2010 to 2015 for Total BLA and Orphan BLA]
CHALLENGES AND THE ROLE OF THE FDA-SCIENCE, REGULATION, AND POLICY
The $64,000 Question

“Why does it take so long to find cures?

Consider this: the potential speed of a high speed train is 200 mph, but the average speed of today’s train is 55 mph. It’s not the speed of the train that holds us back, it’s the state of the track. We need to build faster tracks for faster cures.”

Greg Simon, FasterCures
Regulatory Challenge

- Orphan drugs held to same evidentiary standard as non-Orphan drugs
- To be approved in US, Orphan drugs must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Substantial evidence of benefit requires:
    - *Adequate and well-controlled clinical study(ies)*
      - designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126)
Challenges in Orphan/Rare Drug Development

- Large heterogeneity in disease pathophysiology
- Poorly understood natural histories and progression
- Few patients are available conducting clinical trials
- Uncertain appropriate duration of treatment
- Lack appropriate endpoints that predict outcomes
- Large heterogeneity in treatment effects
- Require compromise, innovation and trade-offs
- Make difficult decisions in absence of ideal information

Proper deployment of Clinical Pharmacology in orphan drug development can extract the most amount of knowledge from least amount of information
Bringing Clinical Pharmacology Tools to Bear

**INNOVATIVE ANALYSES**
- Improved Computing Resources
- Quantitative drug-disease-trial models
- Exposure-response models

**INNOVATIVE TRIAL DESIGNS**
- Clinical trial simulations
- Enrichment, adaptive, dose-response

**KNOWLEDGE MANAGEMENT**
- Leverage prior data
The FDA’s “DUAL” Role

Regulations provide room for flexibility in the review of treatments for rare diseases and the application of regulatory standards...i.e., good scientific judgment
Flexibility in Effectiveness Standard

Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs
Cataloguing FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders
by Frank J. Sasinowski, M.S., M.P.H., J.D.
Chairman of the Board
National Organization for Rare Disorders

http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphanDrugs.pdf
While illustrative in the approaches used, the report is lacking in that, as is often the case, the FDA convened an Advisory Committee to discuss the data and to weigh in on what was an appropriate evidentiary standard for approval in this situation.
QUO VADIS?
Rare Diseases: Common Issues in Drug Development Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5600 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Jonathan Goldsmith at 240-402-9950, or (CBER) Office of Communication, Outreach, and Development at 890-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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August 2015
Rare Diseases
FDA-IOM Report

As an overarching goal, the report, Rare Diseases and Orphan Products: Accelerating Research and Development, calls for implementing an integrated national strategy to promote rare diseases research and product development. The strategy would include seven key elements:

1. Active involvement and collaboration by a wide range of public and private interests, including government agencies, commercial companies, academic institutions and investigators, and advocacy groups.

2. Timely application of advances in science and technology that can make rare diseases research and product development faster, easier, and less expensive.

3. Appropriate use and further development of trial design and analytic methods tailored to the special challenges of conducting research on small populations.
4. Creative strategies for sharing research resources and infrastructure to make good and efficient use of scarce funding, expertise, data, biological specimens, and participation in research by people with rare conditions.

5. Reasonable rewards and incentives for private-sector innovation and prudent use of public resources for product development when the latter appears to be a faster or less costly way to respond to important unmet needs.

6. Adequate organization and resources, including staff with expertise on rare diseases research and product development, for the public agencies that fund biomedical research on rare diseases and regulate drugs and medical devices.

7. Mechanisms for weighing priorities for rare diseases research and product development, establishing collaborative as well as organization-specific goals, and assessing progress toward these goals.
FDA-NIH Collaboration

Therapeutics for Rare and Neglected Diseases (TRND)

The TRND program supports pre-clinical development of therapeutic candidates intended to treat rare or neglected disorders, with the goal of enabling an Investigational New Drug (IND) application. Learn more.

About TRND

TRND supports pre-clinical development from lead optimization through IND application.
- Program Goals
- Operational Model
- TRND in Action
- Frequently Asked Questions

Scientific Capabilities

TRND offers world-class in-house expertise and connections to external resources.
- TRND Expertise
- TRND Resources

Work with TRND

Partner with TRND to create and implement a therapeutic project plan for in-kind resources.
- How to Request a Collaboration
- Considerations for Collaborators
- Intellectual Property
- Project Implementation and Conduct
- Updates to Prior Proposals

TRND Projects

Explore active and completed therapeutic development projects supported by TRND, including projects with clinical activities.
- Active Projects
- Completed Projects
- Clinical Research Studies

TRND Facts

There are more than 6,500 identified rare and neglected diseases, yet only about 250 treatments are available for these conditions. One reason is that limited numbers of patients can make gathering information and designing drug studies difficult. As a result, scientists often know little about the symptoms and biology of these conditions. Another obstacle is that some private companies may find it difficult to justify the cost of developing drugs for such small rare disease markets. Even in the case of infectious diseases — such as malaria — that inflict health burdens on large numbers of people in the developing world, the private sector often neglects therapeutic development because of insufficient economic incentives. Learn more about TRND.
FDA-TRND Collaboration

TRND Resources

Internal Resources
As part of the NIH Intramural Research Program, the TRND program also has access to shared resources on the NIH campus in Bethesda, Maryland, including small and large animal facilities and the NIH Clinical Center, the world's largest facility dedicated to clinical research.

External Resources
The external TRND network includes organizations across the rare diseases patient community and, through close collaboration with the Food and Drug Administration, regulatory experts.

In situations where TRND internal resources are insufficient to generate key materials or data, such as Good Manufacturing Practice production and multi-species Good Laboratory Practice toxicology studies, NCATS leverages its government contracting capability to work with expert contract research organizations.
In October 2011, FDA awarded $2 million to launch Centers of Excellence in Regulatory Science and Innovation at the University of Maryland and Georgetown University. The investment is part of FDA’s effort, outlined in the Agency's strategic plan, to foster a robust, collaborative, regulatory science culture that enables FDA to address the scientific challenges presented by revolutions in medical product development and to improve food safety and quality. In 2014 two new centers were established in collaboration with the FDA.
In our rapidly evolving scientific landscape, the complexity of the Food and Drug Administration’s primary charge – to safeguard the health and well-being of the public through the application of scientifically sound regulatory activities – is constantly being challenged.

The CERSI program was created to provide institutions with a valued opportunity to work directly with regulators while simultaneously providing the FDA opportunities for access and exposure to advanced scientific exchange and training focused on the FDA’s priority areas. As one of the world’s leading institutions in higher education, Johns Hopkins University is pleased to collaborate with the FDA in the development of fundamental new knowledge and tools to advance regulatory science.
CONCLUDING THOUGHTS
Development of Safe and Effective Drugs For ALL Requires a Team Effort

Benefits To All

- FDA Science & Policy
- International Collaboration
- Industry
- Academia
- Patient Advocacy
we cannot solve our problems with the same thinking we used when we created them

~ Albert Einstein
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