Don't Do Different Things…*Do Things Differently!*
Drug Development in Rare Diseases

Regulatory Perspectives on the Approval of Drugs for Rare Diseases

ASCPT ANNUAL MEETING 2016

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CDER/FDA

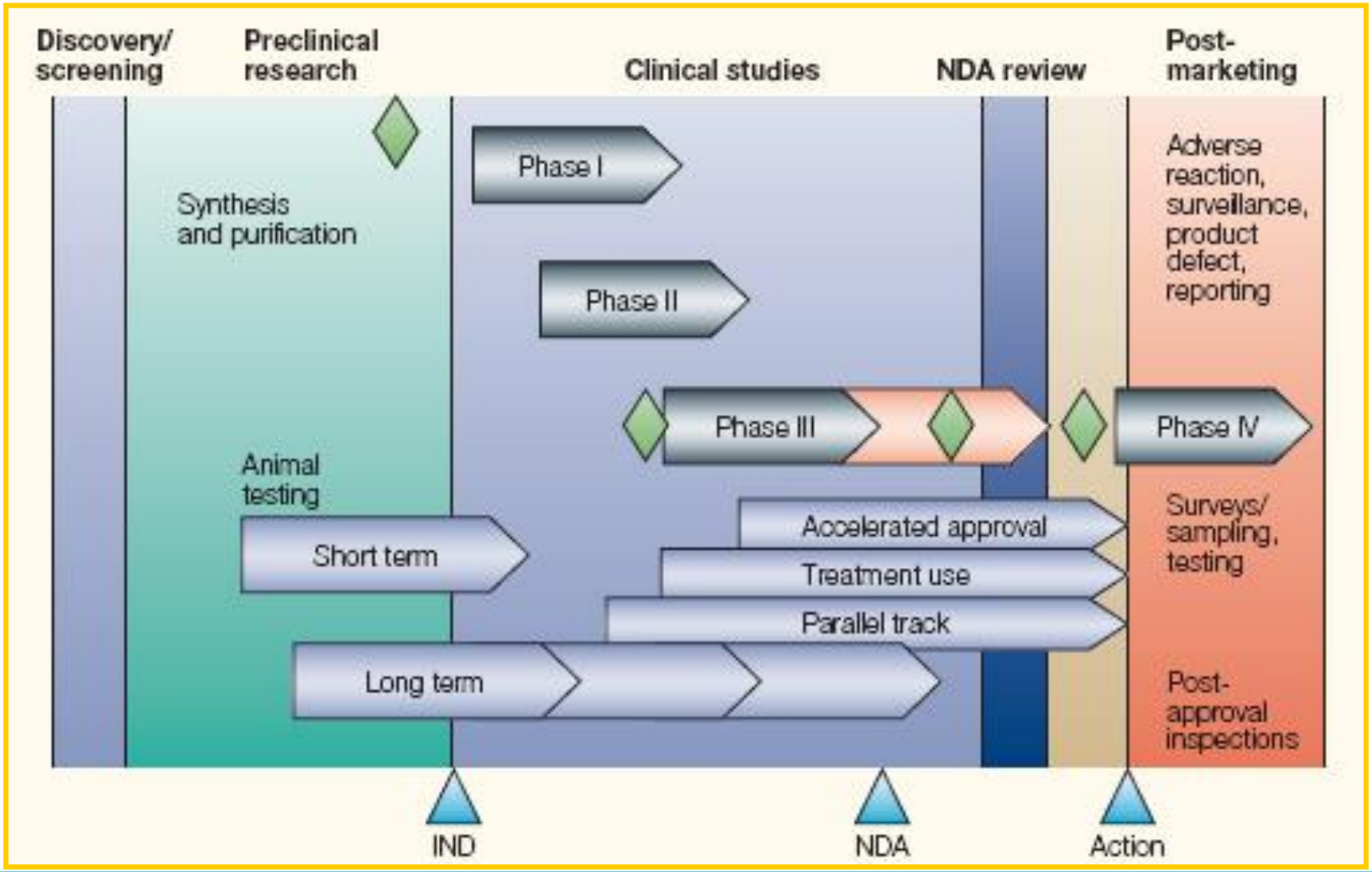
Disclaimer: The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the US Food and Drug Administration.

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

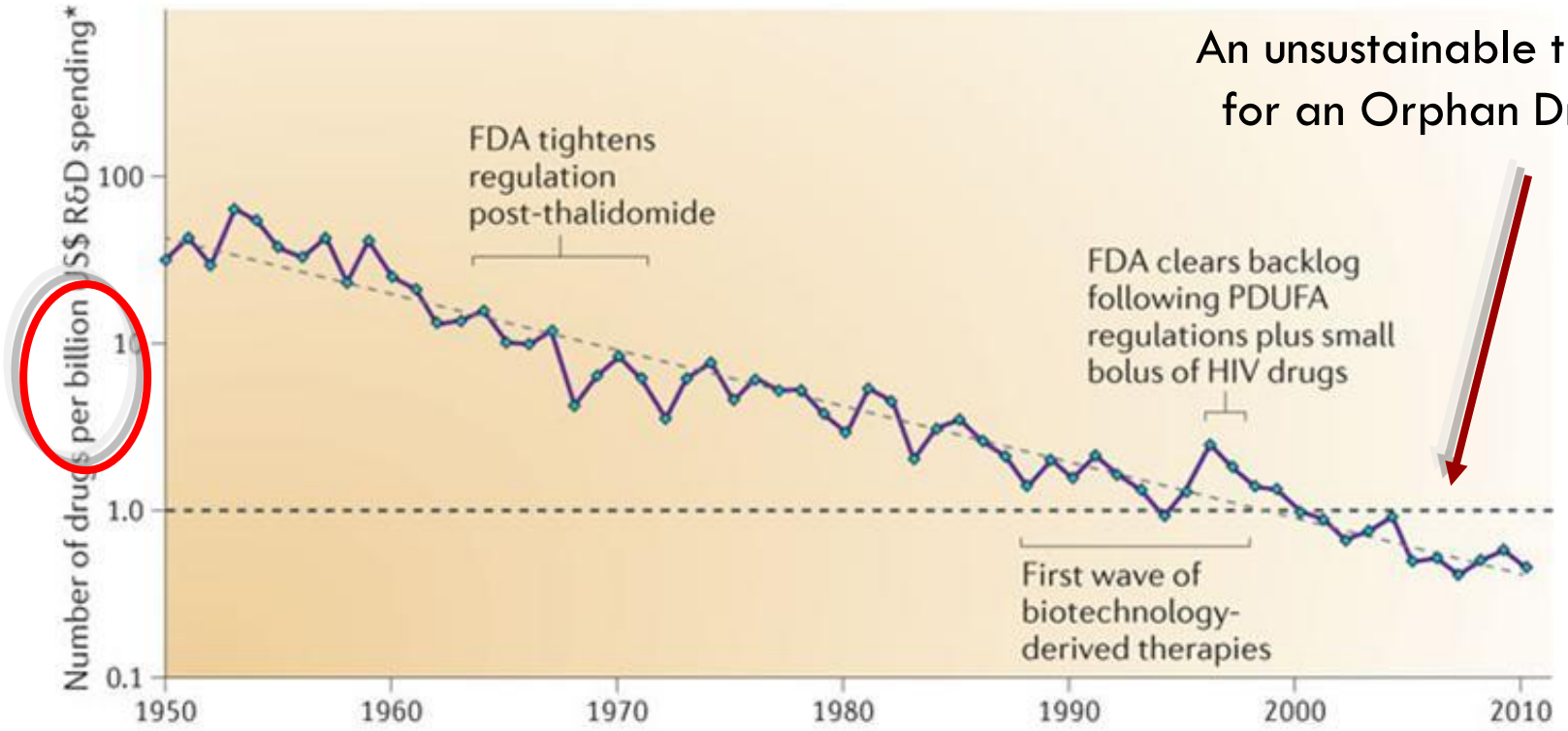
DRUG DEVELOPMENT AND ORPHAN DRUGS/RARE DISEASES IN THE UNITED STATES: AN OVERVIEW

Chronology of Drug Development for Classical and Orphan Drug



Nature Reviews and Drug Discovery, 2003, Volume 2, Page 71

Trends in Drug Discovery



Scannell, JW, et al "Diagnosing the decline in pharmaceutical R&D efficiency" Nature Reviews Drug Discovery, 11:191-200 (March 2012)

Pre Orphan Drug Act: 1982

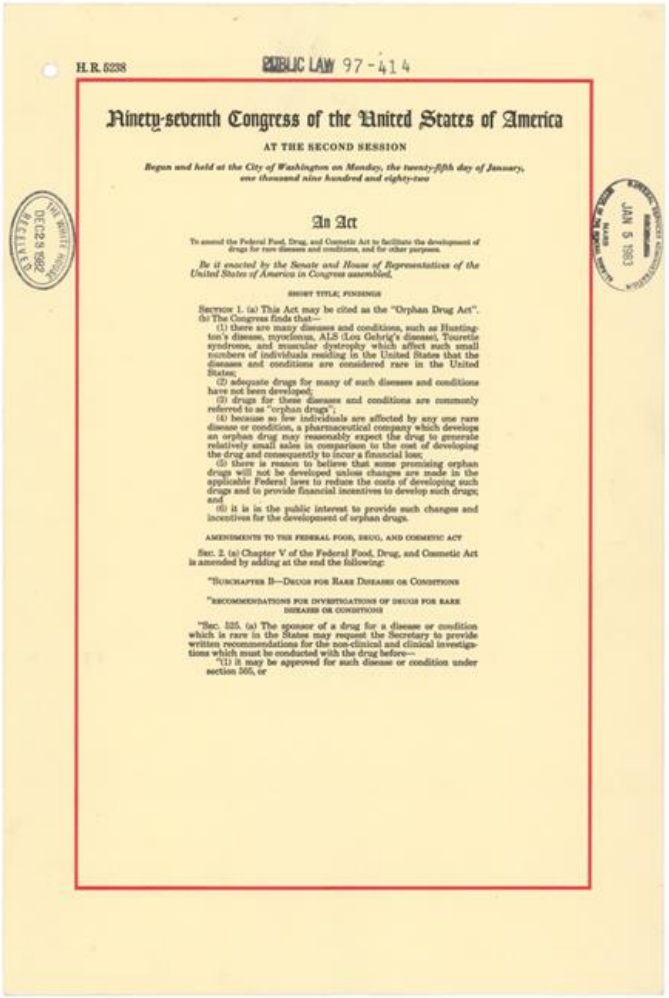
- 1973-1982: 10 new drugs for rare diseases
  - Little economic incentive for large pharmaceutical companies to pursue rare disease indications

- ≈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



H.R. 5238 PUBLIC LAW 97-414

Ninety-seventh Congress of the United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the twenty-fifth day of January, one thousand nine hundred and eighty-two

An Act

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE; FINDINGS

SECTION 1. (a) This Act may be cited as the "Orphan Drug Act".

(b) The Congress finds that—

(1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;

(2) adequate drugs for many of such diseases and conditions have not been developed;

(3) drugs for these diseases and conditions are commonly referred to as "orphan drugs";

(4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;

(5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and

(6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

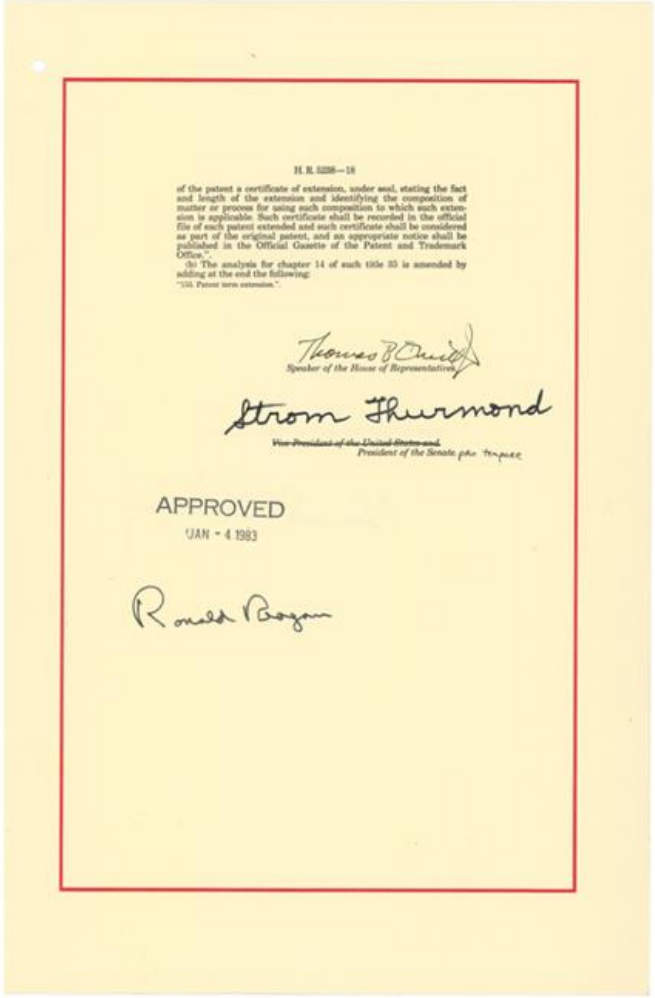
SEC. 2. (a) Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end the following:

"SUBCHAPTER B—DRUGS FOR RARE DISEASES OR CONDITIONS

"RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS

"SEC. 525. (a) The sponsor of a drug for a disease or condition which is rare in the States may request the Secretary to provide written recommendations for the non-clinical and clinical investigations which must be conducted with the drug before—

"(1) it may be approved for such disease or condition under section 505, or



H. R. 5238—18

of the patent a certificate of extension, under seal, stating the fact and length of the extension and identifying the composition of matter or process for using such composition to which such extension is applicable. Such certificate shall be recorded in the official file of such patent extended and such certificate shall be considered as part of the original patent, and an appropriate notice shall be published in the Official Gazette of the Patent and Trademark Office.".

(b) The analysis for chapter 14 of such title 35 is amended by adding at the end the following:

"535. Patent term extension.".

Thomas P. O'Neill
Speaker of the House of Representatives

Strom Thurmond
~~Vice President of the United States and~~
President of the Senate pro tempore

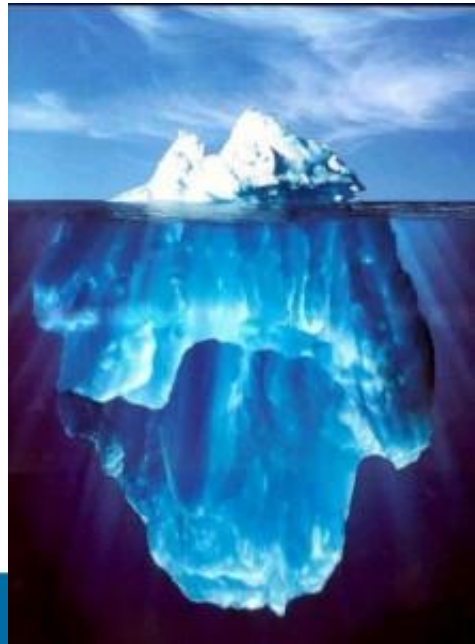
APPROVED
JAN - 4 1983

Ronald Reagan

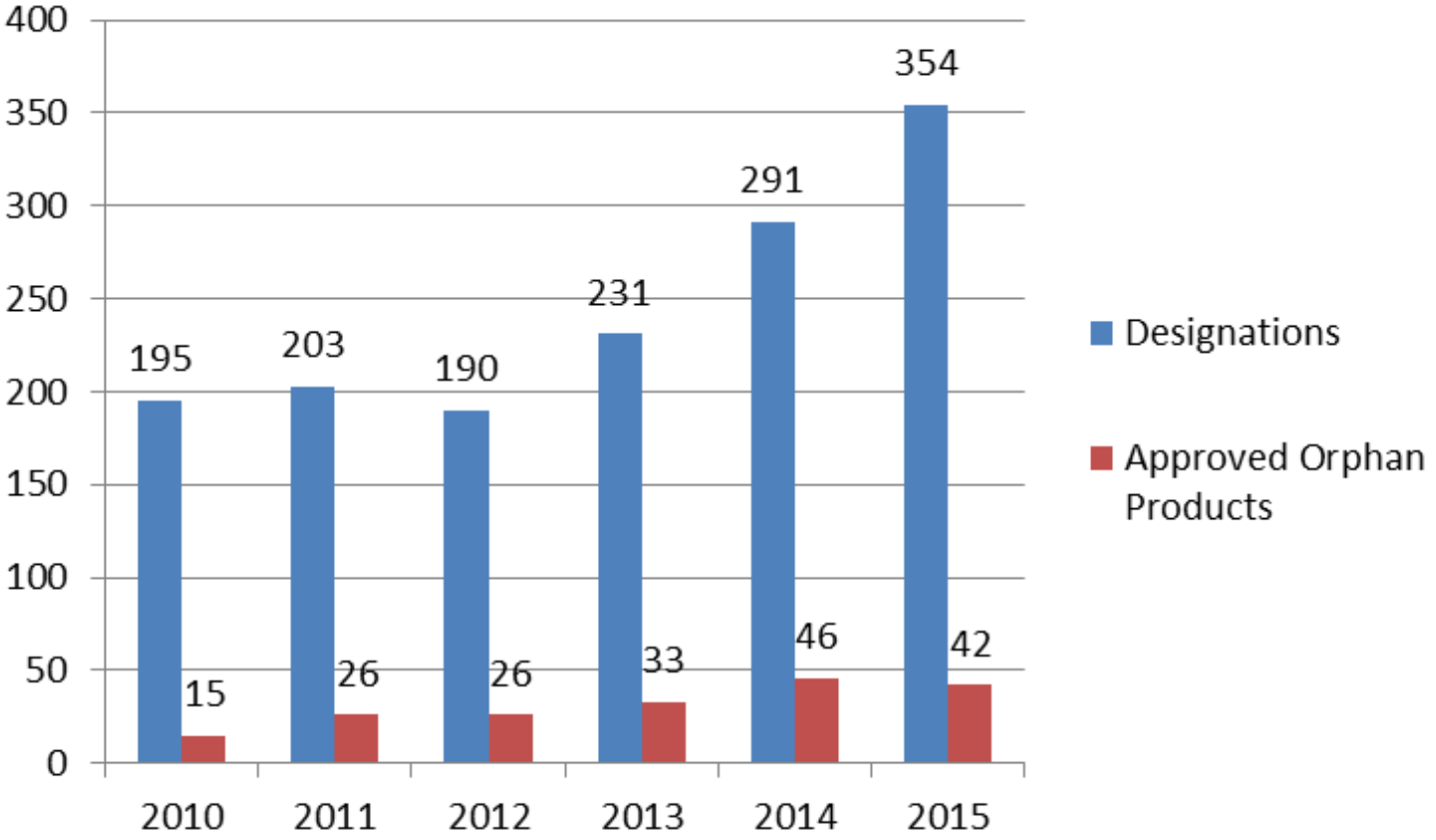
1983 ORPHAN DRUGS/RARE DISEASE DEVELOPMENT –PROBLEM SOLVED?

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……..

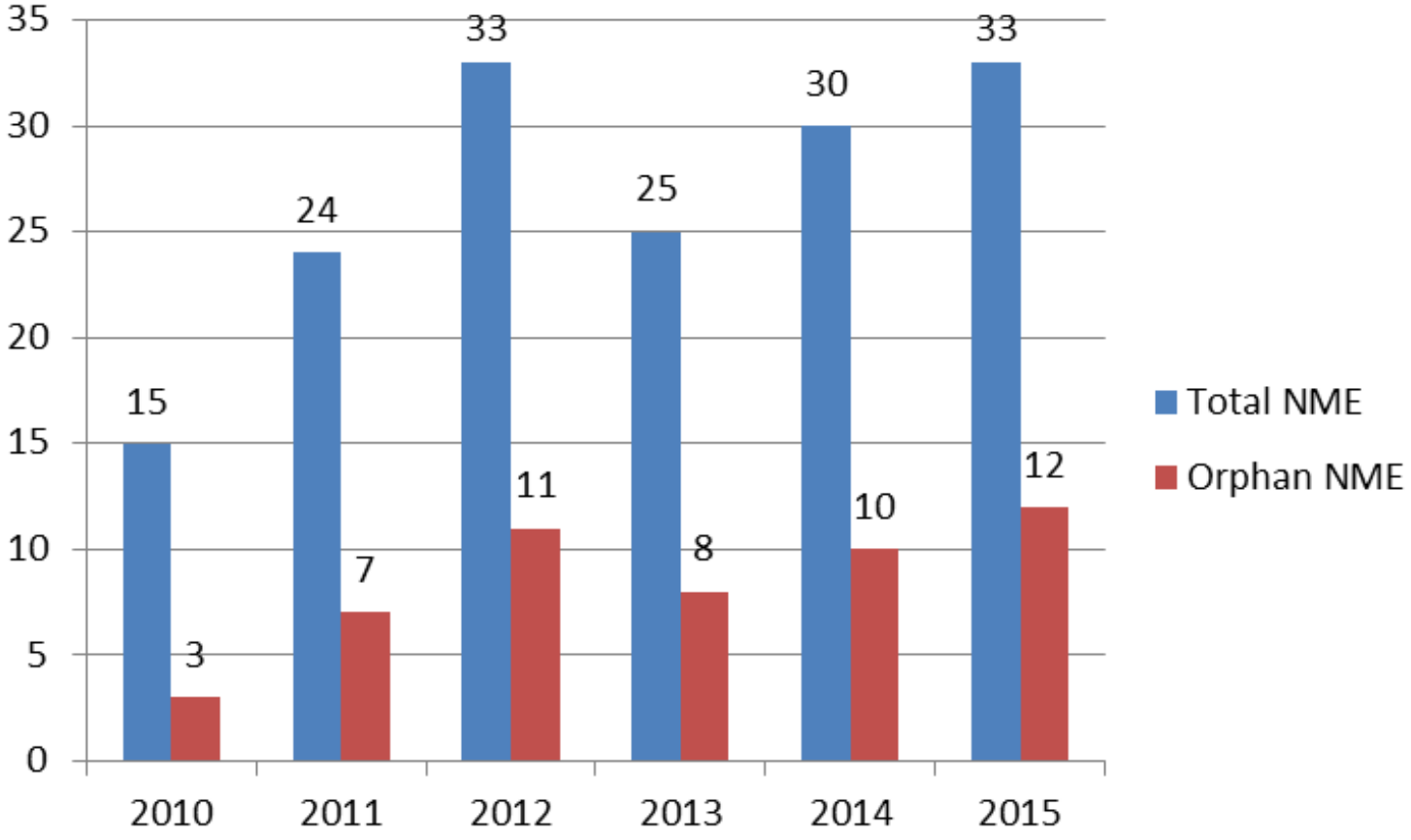


Orphan Designations vs TOTAL Orphan Approvals*

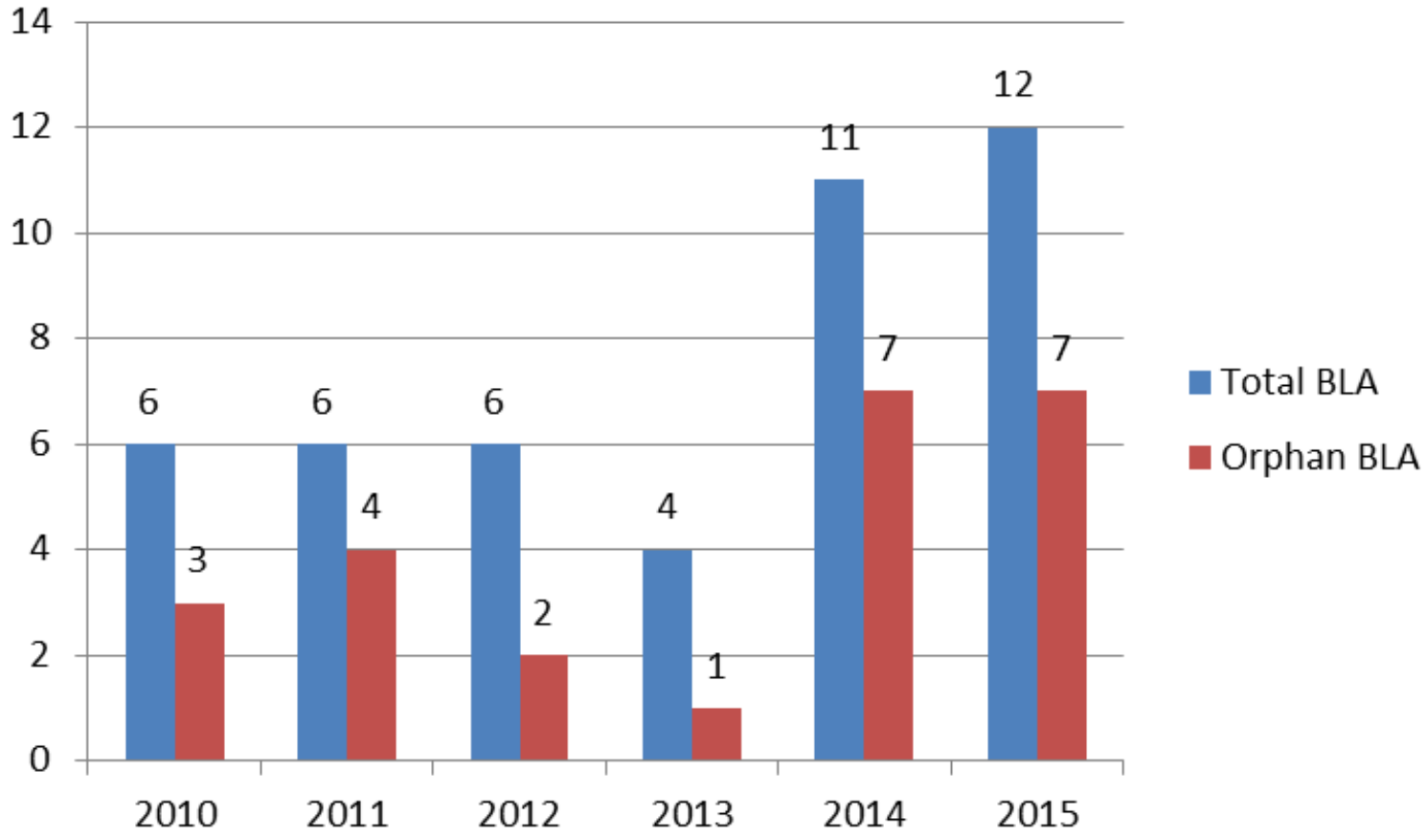


*Includes Orphan Indications for Approved Drugs (re-purposing)

NME/NDA Approvals: Total vs Orphan



NME-BLA Approvals: Total vs Orphan



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

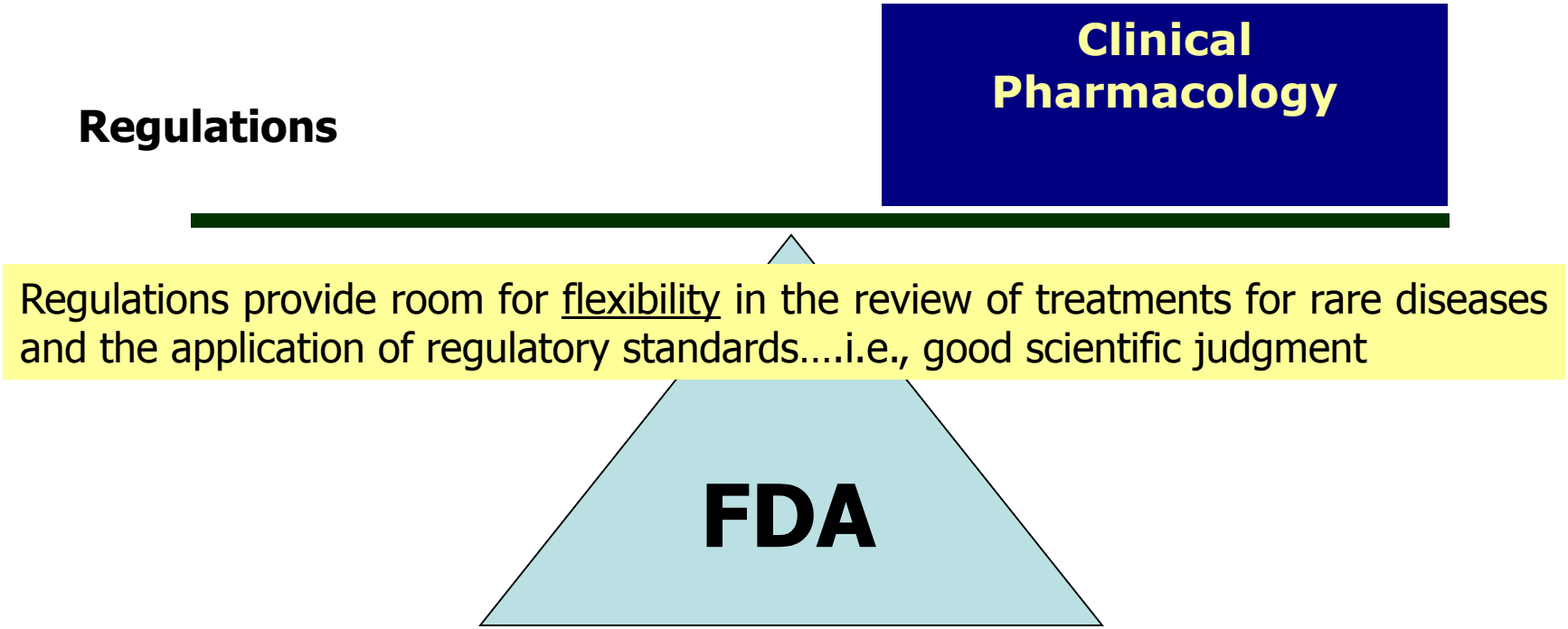
INNOVATIVE TRIAL DESIGNS

- Clinical trial simulations
- Enrichment, adaptive, dose-response

KNOWLEDGE MANAGEMENT

- Leverage prior data

The FDA's "DUAL" Role



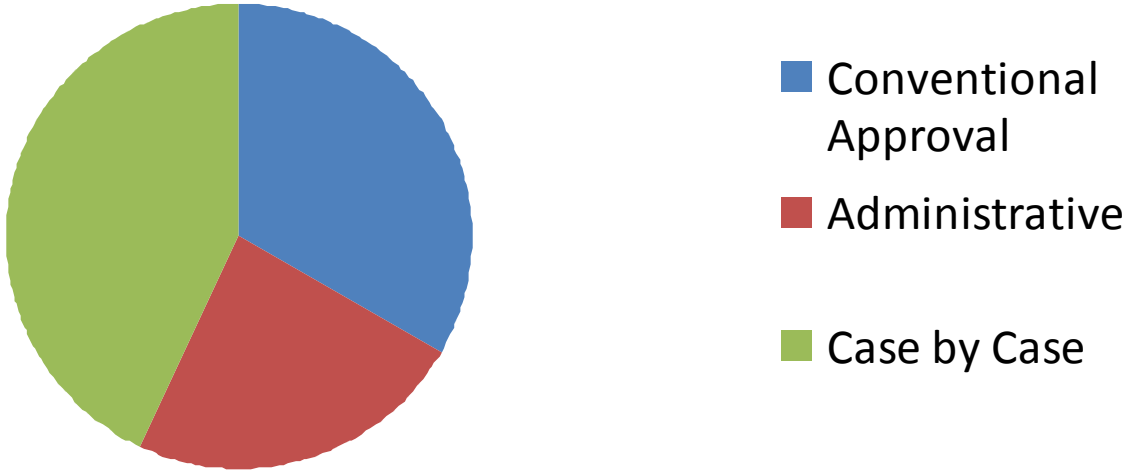
Regulations provide room for flexibility in the review of treatments for rare diseases and the application of regulatory standards….i.e., good scientific judgment

Flexibility in Effectiveness Standard

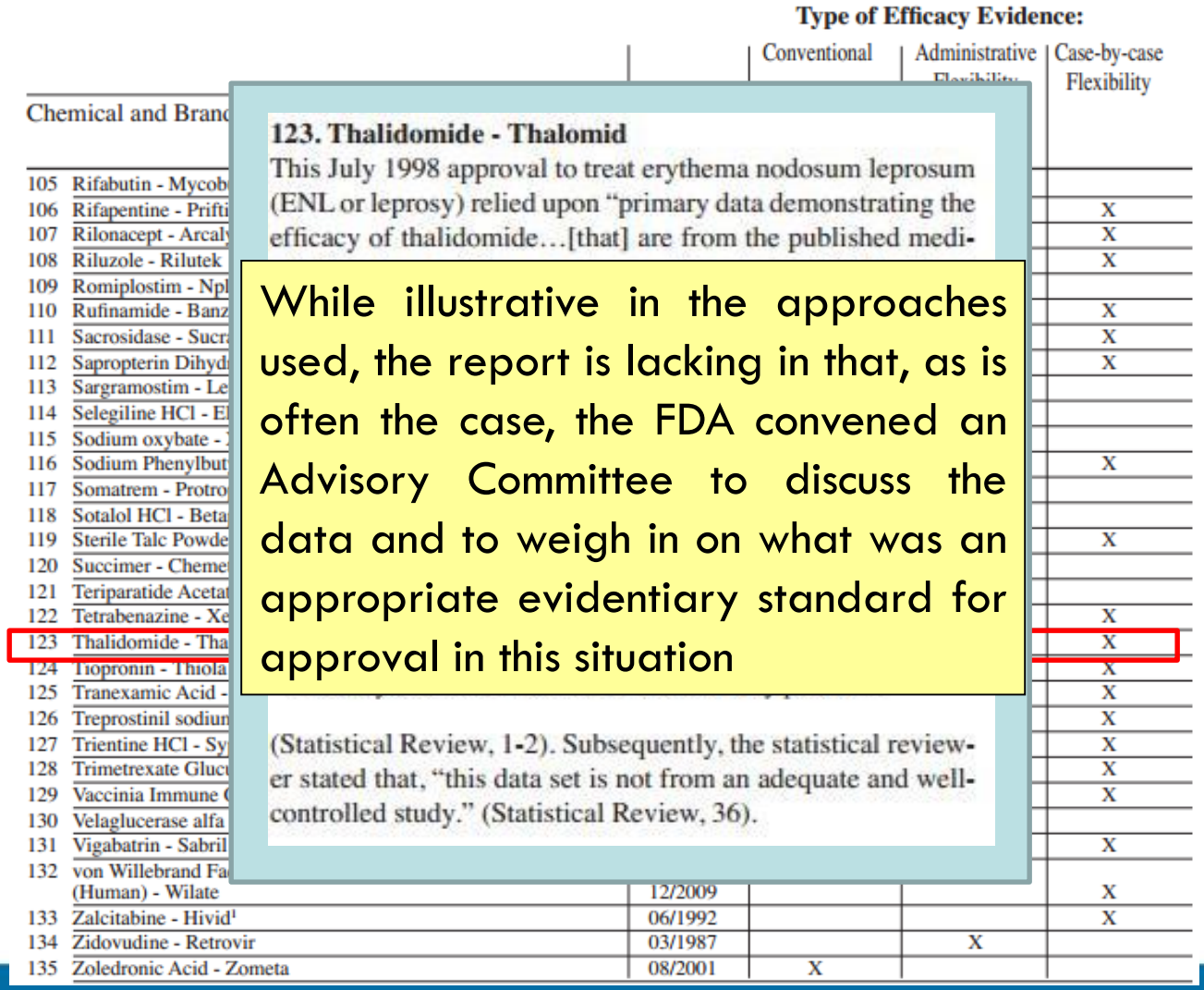
Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs

Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders

by Frank J. Sasinowski, M.S., M.P.H., J.D.[1]
Chairman of the Board
National Organization for Rare Disorders



Flexibility in Effectiveness Standard



	Chemical and Brand		Type of Efficacy Evidence: Conventional	Administrative Flexibility	Case-by-case Flexibility
105	Rifabutin - Mycob				
106	Rifapentine - Prifti				X
107	Rilonacept - Arcaly				X
108	Riluzole - Rilutek				X
109	Romiplostim - Npl				
110	Rufinamide - Banz				X
111	Sacrosidase - Sucra				X
112	Sapropterin Dihyd				X
113	Sargramostim - Le				
114	Selegiline HCl - El				
115	Sodium oxybate -				
116	Sodium Phenylbut				X
117	Somatrem - Protro				
118	Sotalol HCl - Beta				
119	Sterile Talc Powde				X
120	Succimer - Cheme				
121	Teriparatide Acetat				
122	Tetrabenazine - Xe				X
123	Thalidomide - Tha				X
124	Tiopronin - Thiola				X
125	Tranexamic Acid -				X
126	Treprostinil sodiun				X
127	Trientine HCl - Sy				X
128	Trimetrexate Gluc				X
129	Vaccinia Immune				X
130	Velaglucerase alfa				
131	Vigabatrin - Sabril				X
132	von Willebrand Fa (Human) - Wilate	12/2009			X
133	Zalcitabine - Hivid[1]	06/1992			X
134	Zidovudine - Retrovir	03/1987		X	
135	Zoledronic Acid - Zometa	08/2001	X		

123. Thalidomide - Thalomid

This July 1998 approval to treat erythema nodosum leprosum (ENL or leprosy) relied upon "primary data demonstrating the efficacy of thalidomide…[that] are from the published medi-

(Statistical Review, 1-2). Subsequently, the statistical reviewer stated that, "this data set is not from an adequate and well-controlled study." (Statistical Review, 36).

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

http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf

QUO VADIS?

Rare Disease Guidance-Common Issues

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, 5630 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 240-402-9959, or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2015
Rare Diseases

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07/29/15

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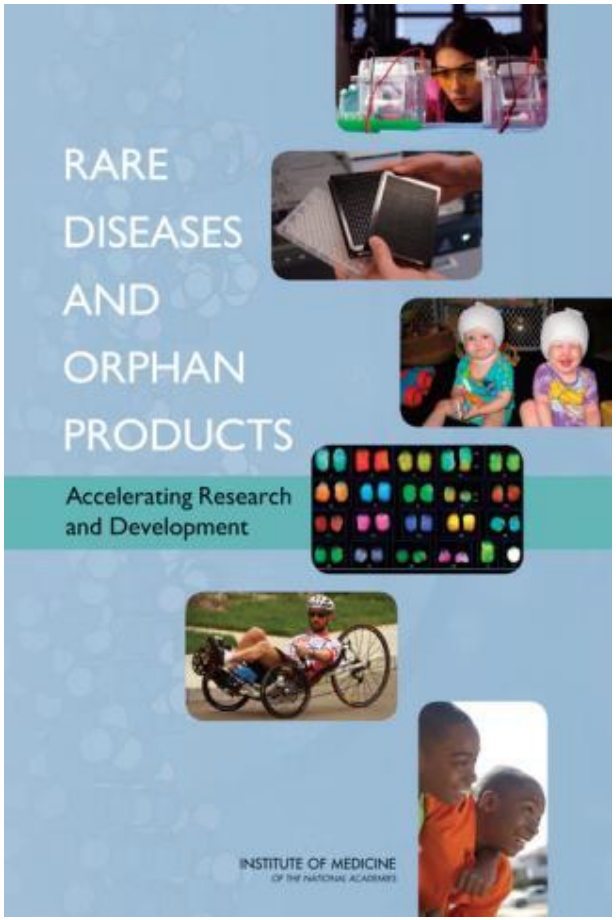
FDA-IOM Report

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.



Released: October 4, 2010

https://iom.nationalacademies.org/Reports/2010/Rare-Diseases-and-Orphan-Products-Accelerating-Research-and-Development.aspx

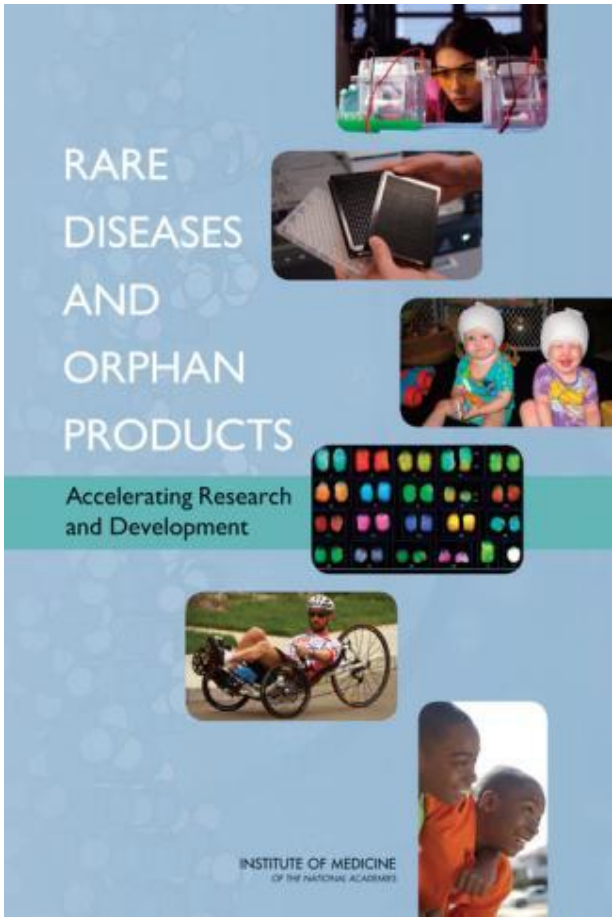
FDA-IOM Report

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.



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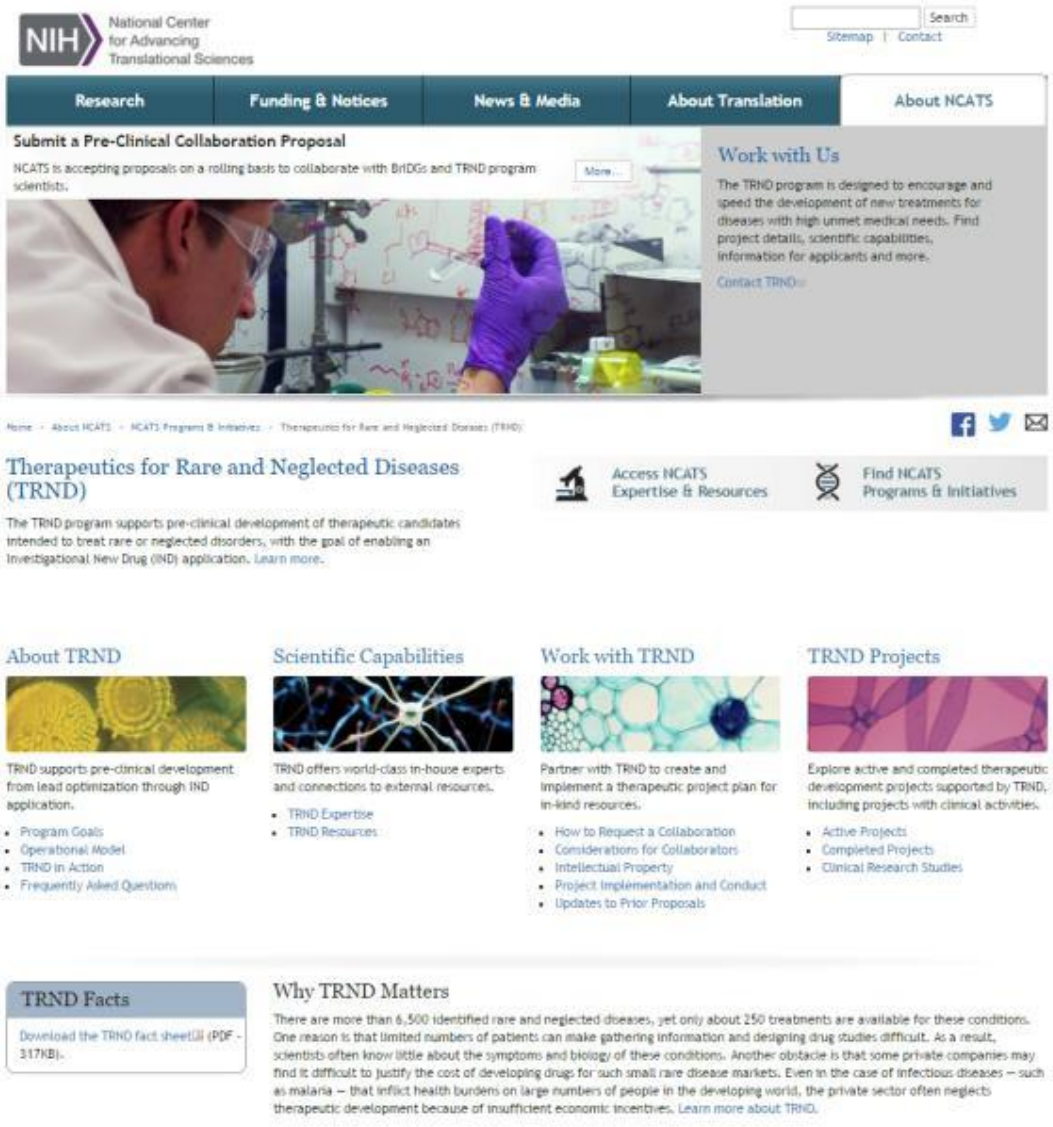
FDA-NIH Collaboration



FDA-TRND Collaboration

National Center for Advancing Translational Sciences

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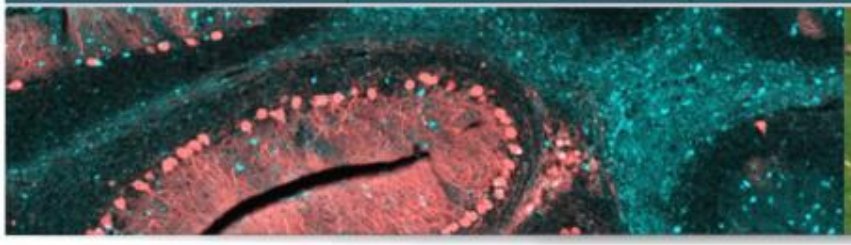

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About TRND

TRND Scientific Capabilities
> TRND Expertise
> TRND Resources

Work with TRND

TRND Projects

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.

Contact

TRND staff

FDA-Academic Collaboration

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.

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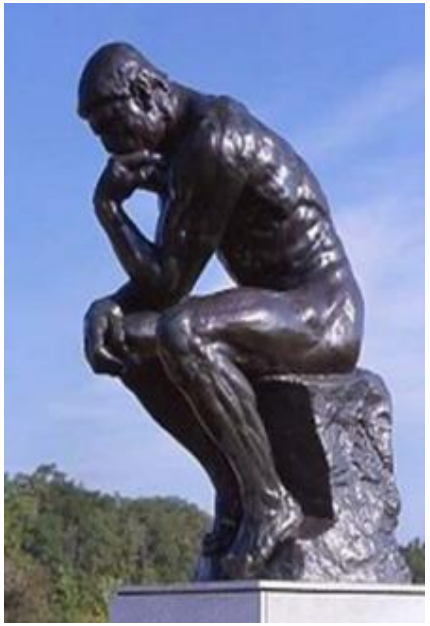
Center of Excellence in Regulatory Science and Innovation

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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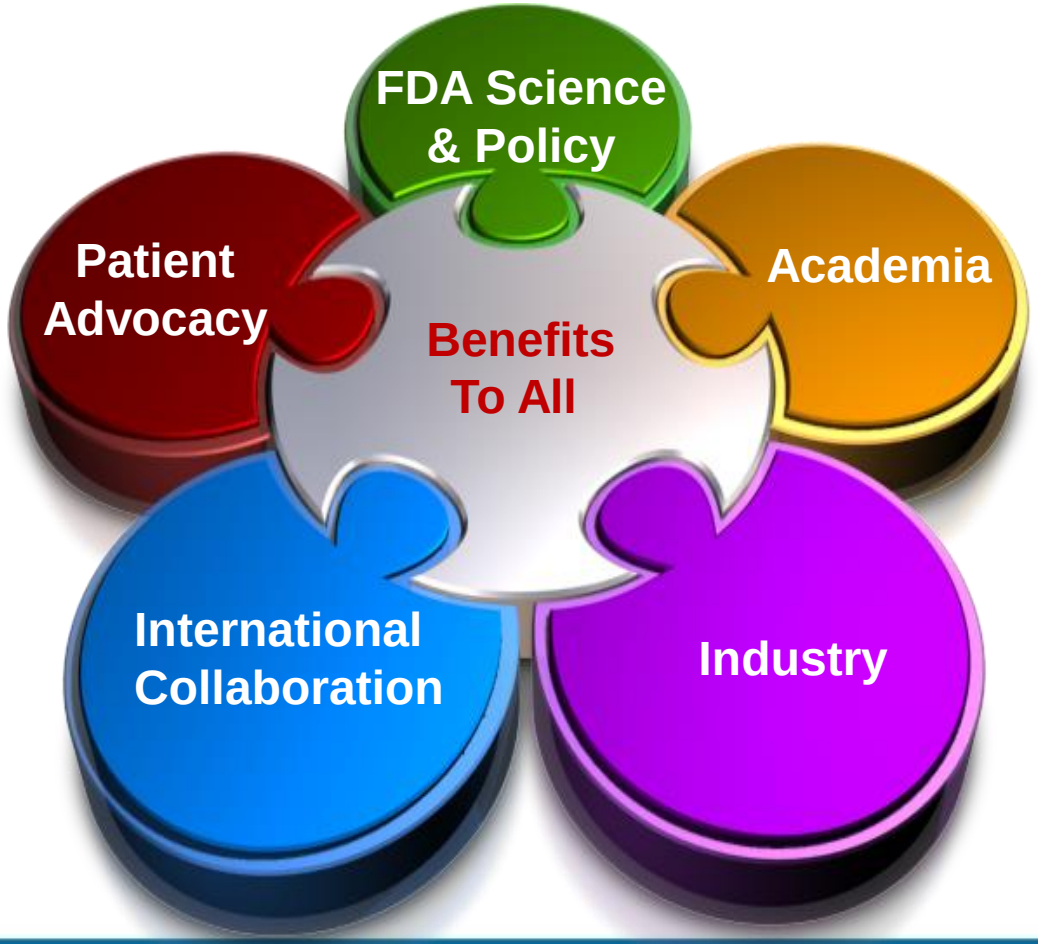
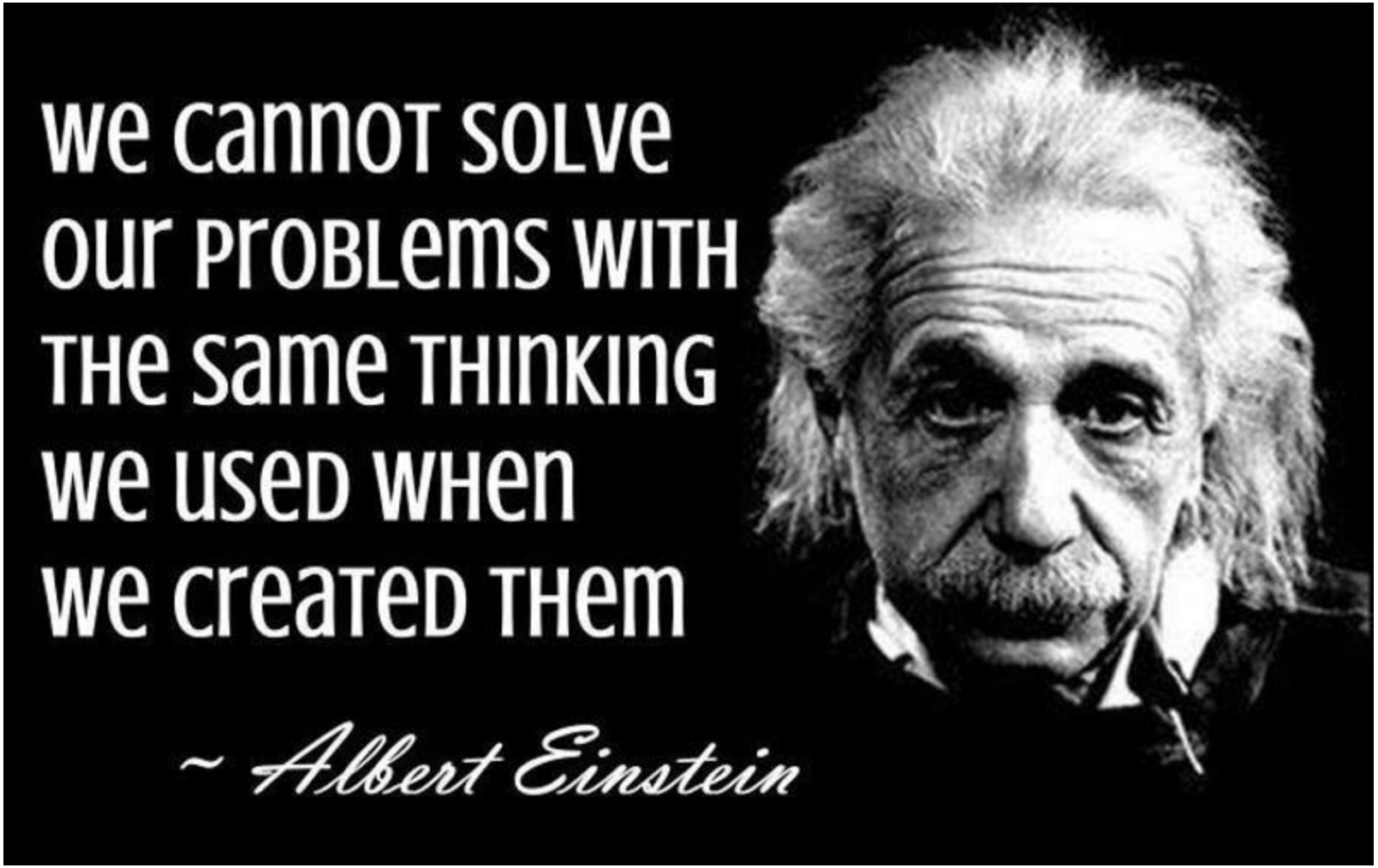
Development of Safe and Effective Drugs For ALL Requires a Team Effort




we cannot solve
our problems with
the same thinking
we used when
we created them
~ Albert Einstein

Contact Information

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