Introduction: Rare Diseases, Orphan Drugs

Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology

March 2, 2011

Dallas, Texas

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Food and Drug Administration

Silver Spring, Maryland

Update and Highlights: 2010-2011

Guidance for Industry

Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Released for public comment on 2/17/11

Advisory Committee's "Strong Encouragement"

By not mandating DNA sample collection, the agency appears to have adopted the consensus view of its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

In 2008, the committee agreed that DNA samples should be collected from all patients in all Phase I-III trials. FDA returned to the committee for further advice in March 2010 because, the agency said, drug developers asserted 100% DNA sample ascertainment was not possible due to differences among how ethics committees, institutional review boards and regulatory health agencies view DNA sample collection and storage processes.

The Pink Sheet Daily on 2/18/11

Other Guidance Updates

- Drug Interaction Studies

- Transporter mediated DDI
- Decision trees for CYP DDI
  - Inhibition and induction
- Multiple co-factors and DDI
  - Use of PBPK
- Drug-protein DDI
- PGx data to inform DDI
- Non-CYP enzyme DDI

Under CDER clearance – anticipate June 2011 release

- Renal Impairment Guidance

- Studies for non-renal routes
- Staging recommendations
  - Clcr (C-G) and MDRD (eGFR)
- Hemodialysis studies
  - Both on and off dialysis
- Renal studies of proteins
- Labeling recommendations
- Address 2010 comments

Anticipate to be sent for clearance in June 2011

What Are They?

- Rare disease = one affecting fewer than 200,000 people in the US
  - 6000-8000 rare diseases affecting 7% of population
  - 4 out of 5 have a genetic basis
  - 70-75% have a prevalence of < 100,000 people

- Orphan drug = one that has been developed to treat a rare disease
  - More than 2200 molecules designated as orphan drugs
  - 30-40% are for rare cancers
  - 362 approved drugs since 1983

http://www.eurodis.org/about-rare-diseases; Tambuyzer, Nat Rev Drug Discovery 2010, 9, 921-929

Orphan Drug Development and Regulatory Challenges

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

Extract most amount of knowledge from least amount of information

National Commitment to Rare Diseases

February 28, 2011

The development of effective medicines for rare diseases is a <u>primary</u> FDA objective

Case For Rare Disease and Orphan Drug Development

- Trends
  - Licensing deals (ex: Pfizer and Protalix)
  - Mergers (ex: Sanofi and Genzyme)
  - Label extension strategies (ex: EPO for anemia in CRF)
  - Government roadmaps (ex: EMA and NIH)
  - Dedicated industry units (ex: GSK and Pfizer)

REPORT BRIEF OCTOBER 2010

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For more information visit www.iom.edu/raredseaseresearch

Rare Diseases and Orphan Products
Accelerating Research and Development

RARE DISEASES AND ORPHAN PRODUCTS
Accelerating Research and Development

Implementing a national strategy…..apply advances in science and technology, innovation in trial design, and incentives for sharing data…..

Categories of Rare Diseases and Orphan Drugs

NME for as yet untreated people with rare disease

-- Example: alglucosidase alfa for Pompe disease (~ 1:40000?)
-- Exogenous source of lysosomal enzyme acid alpha-glucosidase (GAA)
-- Muscle weakness, enlarged hearts, difficulty walking

Drug for common disease → Drug for rare disease ("re-purpose")

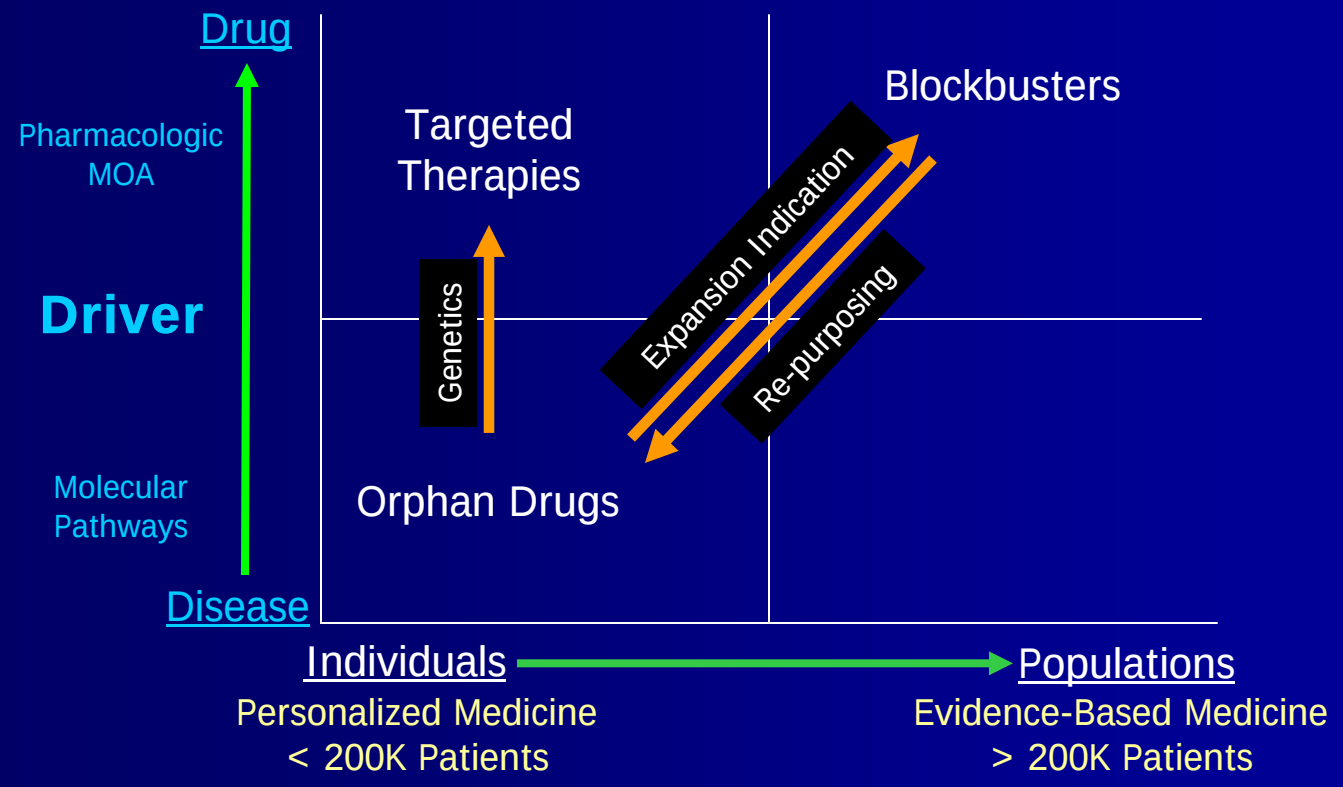
-- Example: sildenafil for pulmonary hypertension (~ 1:50*?)
-- Selective inhibitor of phosphodiesterase type 5 (cardiac biomarkers)
-- SOB, chest pain, tachycardia, ankle/leg swelling

Drug for rare disease → Drug for common disease

-- Example: canakinumab for Muckel-Wells syndrome (~ 1:2000?)
-- Anti-interleukin-1 beta monoclonal antibody (protein biomarkers)
-- Fever, rash, conjunctivitis, swollen joints, hearing loss, renal failure

* Severe pulmonary hypertension after pediatric cardiac surgery as opposed to idiopathic PH

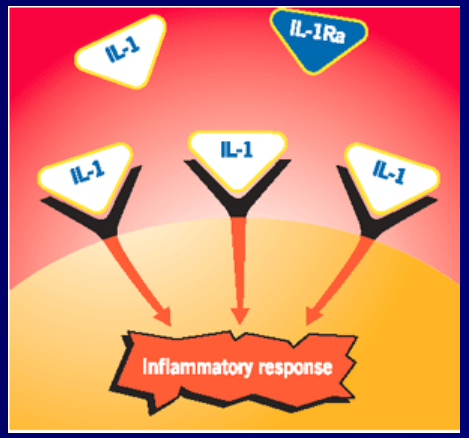
Contrasting Product Development: Disease-Driven vs Drug-Driven



Adapted from J Pharm Bio Sciences 2010 (2), 4:290-299

General Model for Development of Orphan Drugs: Step 1

- Establish linkage between the biological MOA of drug and molecular basis of disease (target ID, get to cures – not only symptom control)

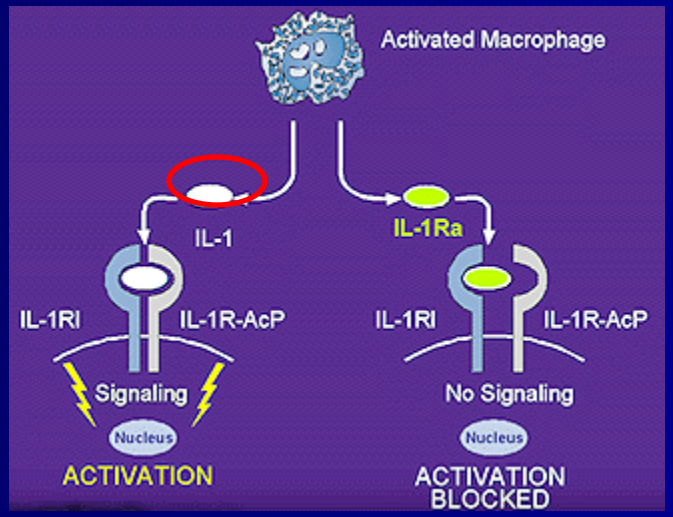


Inhibition of IL-1 – inflammatory mediator – in synovial fluid of joints can reduce the signs and symptoms of CAPS and RA. IL-1 receptor antagonists can block the effects of over-abundance of IL-1 (causal pathway)

Adapted from Cohen, Nat Rev Drug Discovery 2010, 9:856-866

General Model for Development of Orphan Drugs: Step 2

- Measure changes in biomarkers that enable proof-of-concept clinical studies of efficacy (supportive evidence and higher efficacy study success rates)



Competitive inhibition of binding of IL-1 by drug

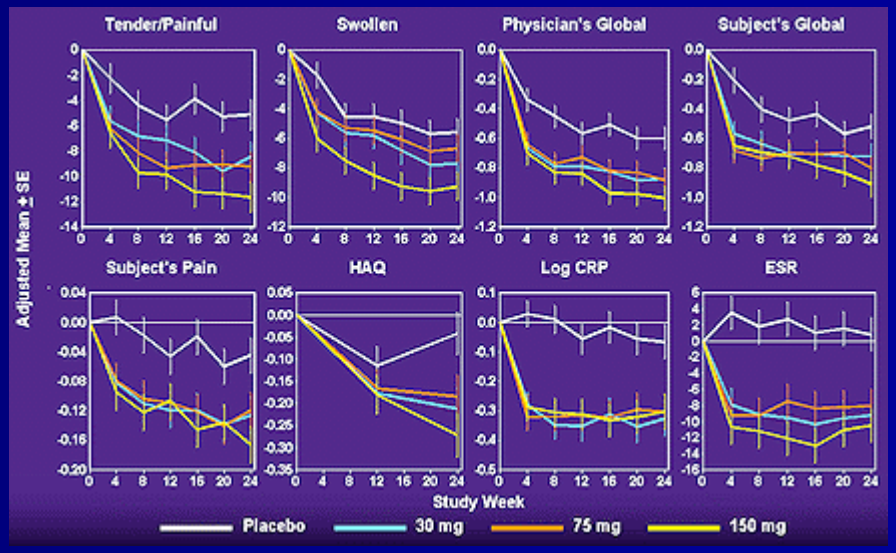
Adapted from http://www.kineretx.com

General Model for Development of Orphan Drugs: Step 3

- Innovative trial designs to validate biomarkers-outcomes and quantitative methods for analysis of data (D/R)

<u>PK/PD models and simulation</u>

Ex: correlation between serum levels of canakinumab and free and total interleukin-1 beta as measured by ELISA in healthy volunteers at more than one dose level



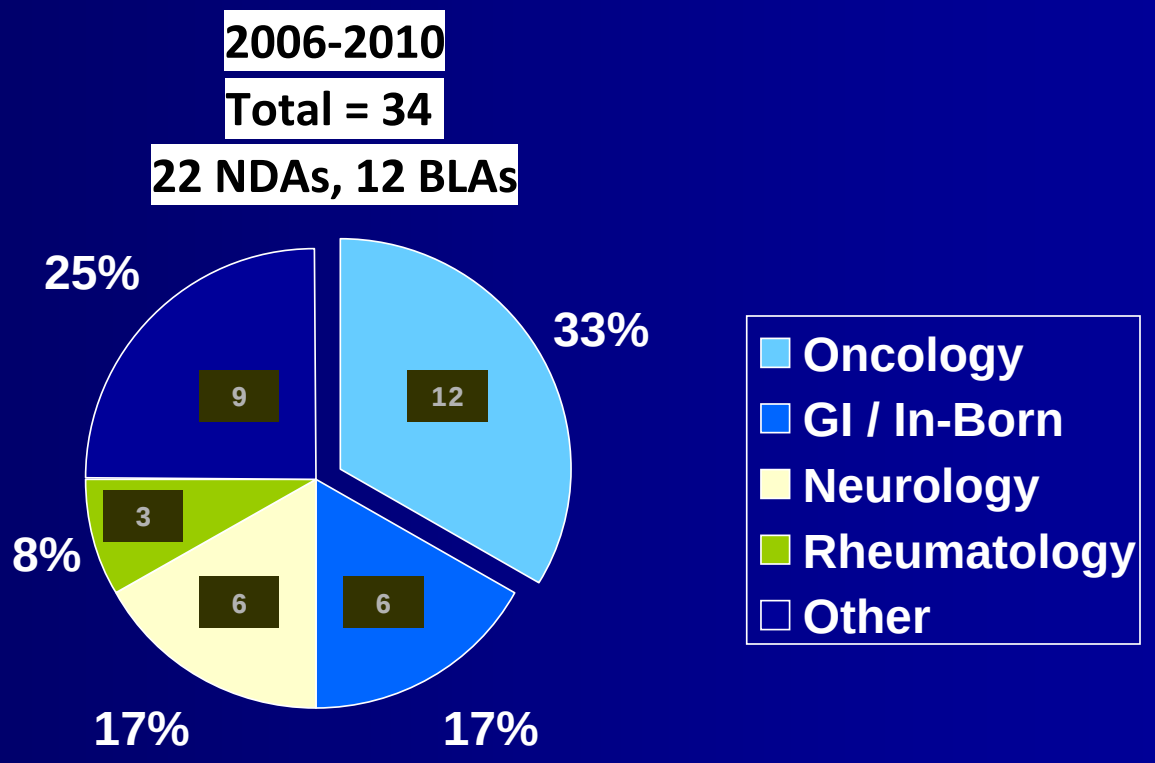
Improvements in 5 clinical response criteria observed as a function of dose

Bonner et al, Ann Congr Eur Resp Soc 2006, 748. Breshnihan et al, Arthritis Rheum, 1998, 41(12), 2196:2204

Development Strategies Are An Evolving Paradigm

- No consensus exists on what constitutes an ideal drug development program ~ no right way
- FDA seen as many different approaches to drug development as there are approved drugs
- Lessons learned from pediatric and oncology drug development can be applied to rare diseases
- Late-stage clinical development programs can be guided by early-phase clinical pharmacology studies using M/S and CTS
- Biomarkers, D/R and PK/PD study data can be persuasive and provide confirmatory evidence of efficacy

Original NDA/BLA Orphan Drug Approvals: Recent Successes

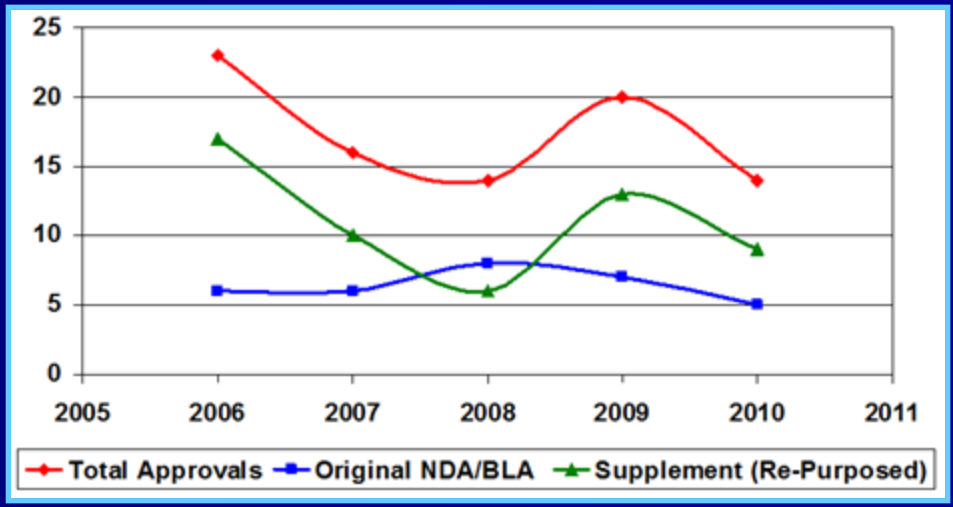


Source: Dennis Bashaw (FDA)

Further Breakdown of NDA/BLA Approvals For 2006-2010

- 34 approvals represented 27 different indications
  - 6 indications had two approvals
- 26 different companies sponsored 34 approvals
  - No sponsor had more than 3 approvals

Original approvals (38%)
Re-purposed approvals (62%)



Source: Dennis Bashaw (FDA)

Orphan Drug Approvals in CDER in 2010

Product	Indication	AP Month 2010	Division	NDA/BLA
Dalfampridine (Ampyra™, Acorda)	Improve walking in Multiple Sclerosis	January	DNP	NDA
Collagenase (Xiaflex™, Auxilium)	Dupuytren's contracture	February	DPARP	BLA
Velaglucerase (VPRIV™, Shire HGT)	Gaucher disease	February	DGP	NDA
Carglumic acid (Carbaglu®, Orphan Europe)	NAGS deficiency (UCD)	March	DGP	NDA
Rifaximin (Xifaxan®; Salix Pharms)	Hepatic encephalopathy	March	DGP	NDA
Alglucosidase alfa (Lumizyme®, Genzyme)	Late-onset Pompe disease	May	DGP	BLA
Glycopyrrulate (Cuvposa™, Shionogi)	Drooling in children with neurologic disorders (e.g., cerebral palsy)	July	DNP	NDA
Pegloticase (Krystexxa™, Savient Pharma)	Chronic gout not responsive to conventional therapy	September	DPARP	BLA

Source: John Jenkins (FDA)

Key Features of CDER Orphan Drug Approvals in 2010

- Diverse collection of diseases and patient populations
- Program size varied from 23 to 540 patients
- Broad range of study designs and development processes
- Relied on both novel and well-established endpoint ~ reliable, meaningful, well-defined and “fit for purpose”
- Wide range of different studies to provide the “totality of evidence” needed for approval

Factors Influencing Success of Orphan Drug Development

- Understand disease pathology (why?)
- Ease of demonstrating proof-of-concept (when?)
- Show linkage between drug and target (where?)
- Delineate drug mechanism of action (how?)
- Clear and identifiable symptoms (who?)

Mechanistic biomarkers as a key scientific foundation

What Has Brought Clinical Pharmacology To This Point?

- Large RCTs and full clinical pharmacology packages are not feasible in developing orphan drugs
- Mechanistic approaches to drug development lend themselves to quantitative analysis
- Advances in pharmacometrics – CTS and use of modeling – has made important contributions to pediatric drug approvals
- Scientifically sound trade-offs between “full” and “light” clinical pharmacology datasets enable oncology drug development
- Well-designed clinical pharmacology studies and innovative data analysis provide substantial evidence of benefit

Important Challenge: Identify Safety Signals With Small Populations

- Clinical studies underpowered to detect serious safety issues given the unmet medical need of rare diseases
- Full assurance needed that benefits outweigh the risks
- Approach safety from off-target pharmacological MOA as opposed to whole organ observations
  - Inform adverse event prediction through aggregation of data on molecule – SA relationships, animal toxicology, human pharmacology – from many sources
  - Apply bioinformatics and systems pharmacology to identify potential off-target molecular pathways
  - Collect safety data preapproval, target surveillance postapproval

Goals for Today: Focus on Role of FDA

"...FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards..."
(CFR314.105)

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

"...and the role that modern clinical pharmacology can play in the application of processes and tools to provide the kind and quantity of data and information applicants need to meet the statutory standards..."

Concluding Thought

"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 speed of the track. We need to build faster tracks for faster cures."

Greg Simon, FasterCures

http://www.fastercures.org/

Orphan Drug Act: History, Perspective and Challenges for the Future

Tim Coté MD MPH

Director, FDA Office of Orphan Products Development

Presented March 2, 2011

CPAC Meeting, Dallas, TX

Orphan 101: The “Growing-est” Sector of All

- The Orphan Drug Act 101---Promise and Product
- So what is an orphan designation all about anyway?
- Subsets---slicing salami or medically relevant?
- OOPD and Review Divisions--Good neighbors with good fences

Economic Realities: 1982

- Rare diseases = Few potential pill buyers
- 1973-1982: 10 new drugs for rare diseases
- ≈7,000 rare diseases; 25 million people
- Congressmen/Senators regularly besieged by requests for assistance/research

Abbey Myer: Grassroots Political Mover

"They are like orphans in that they require special care." Henry Waxman

NORD
National Organization

The New Deal of the ODA

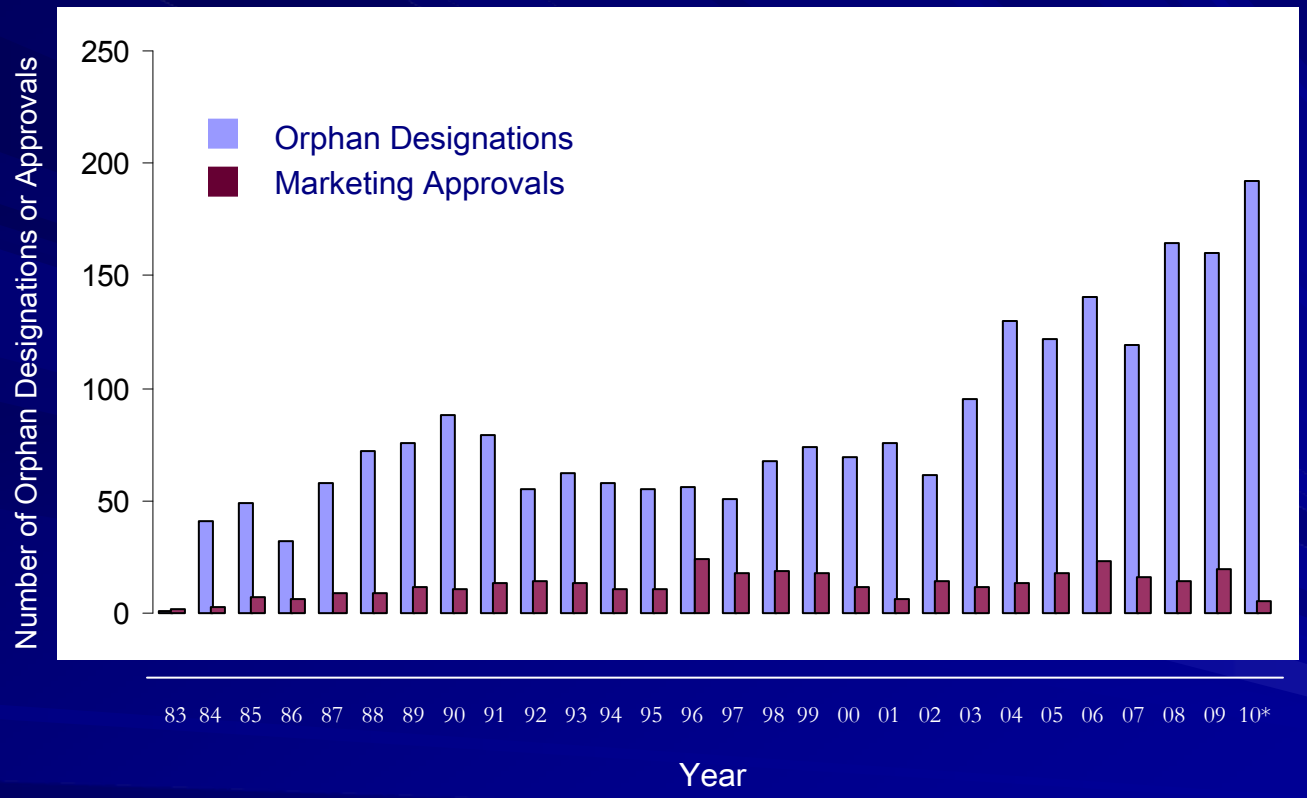
- Get a drug designated as an “orphan drug”
  - Show (with data) that it’s “promising”
  - For treating <200,000 person in the US
- Do the clinical trails/get marketing approval
- Receive incentives:
  - MARKET EXCLUSIVITY
  - Tax credits
  - Fee exemptions

ODA: A ***MAJOR SUCCESS***

- 362 Approved Drugs
- ≈2,250+ Designated Orphan Drugs
- 2008: 38% of all FDA-approved NMEs were Orphans

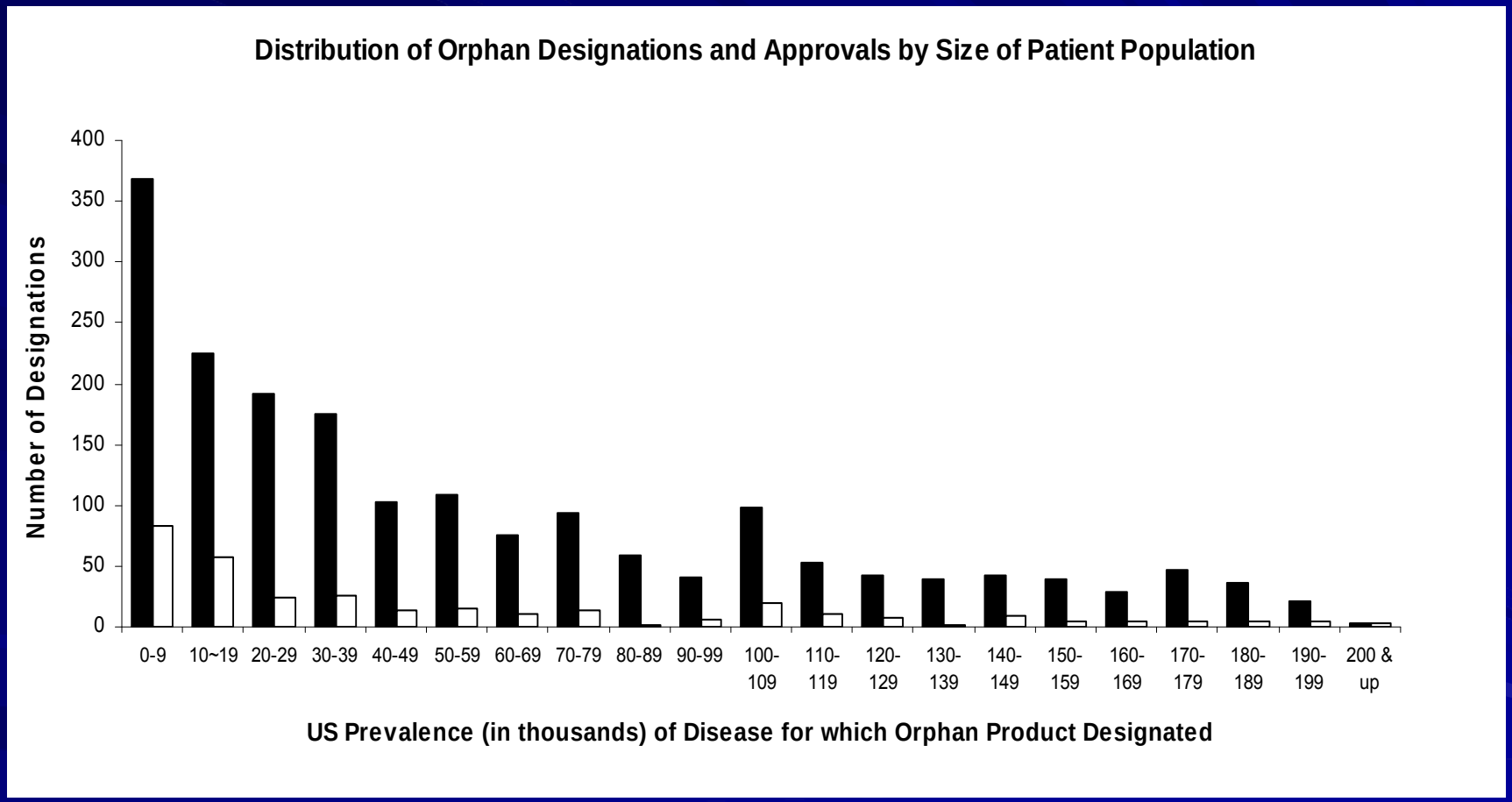
The US Orphan Drug Act has been HUGELY Successful

Number of orphan designations and marketing approvals from 1983-2010



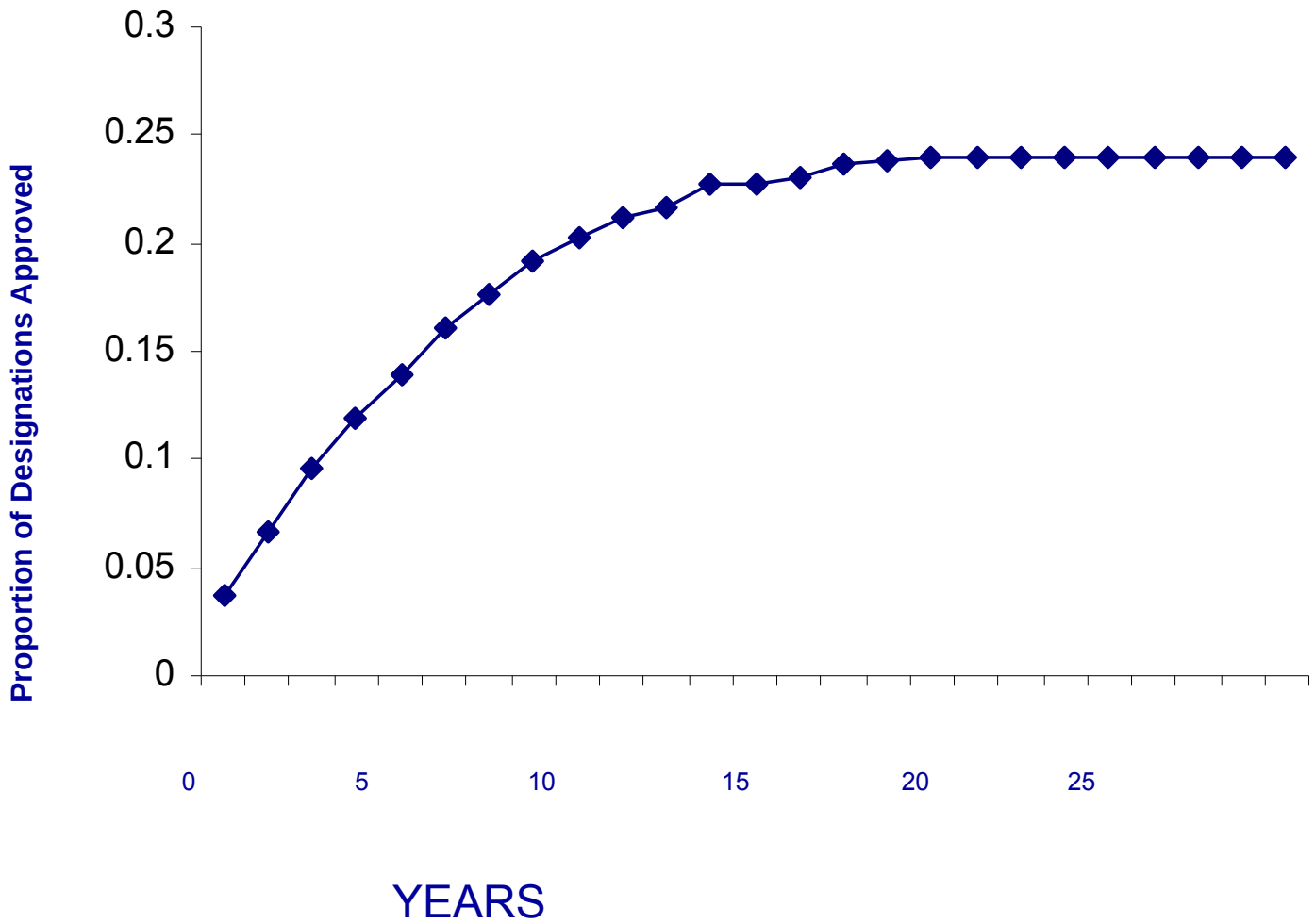
* The database is currently being updated to include new marketing approvals for 2010. However, the number of designations for 2010 (192) is accurate.

The Diseased Populations Served have been VERY Small



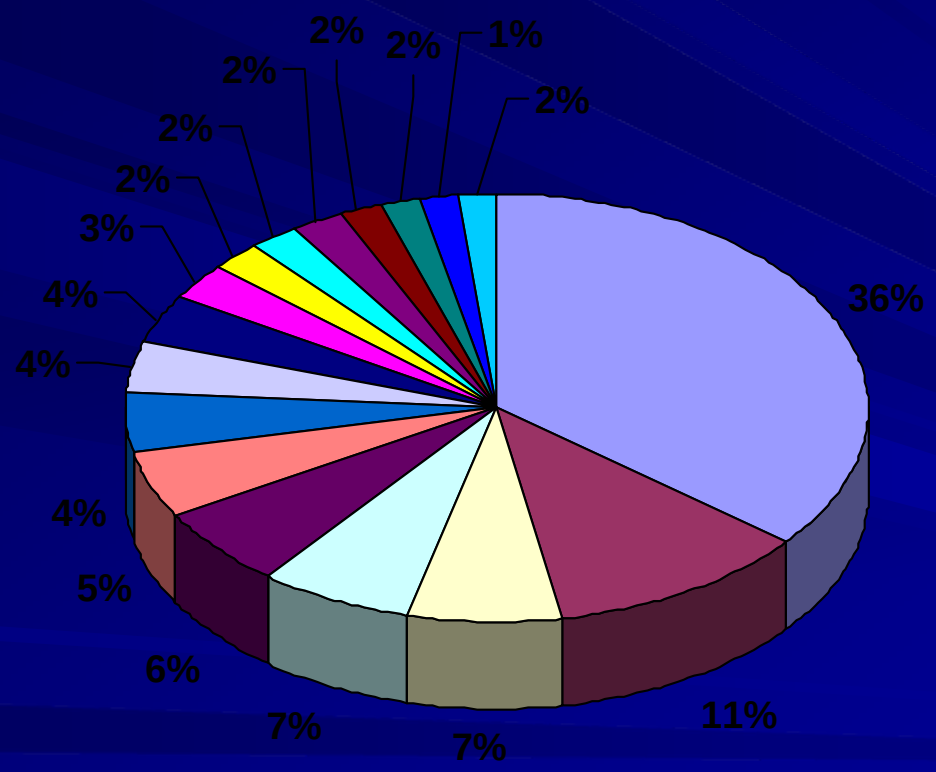
Source: FDA/OOPD, M. Braun et al

Time from Designation to Market Approval



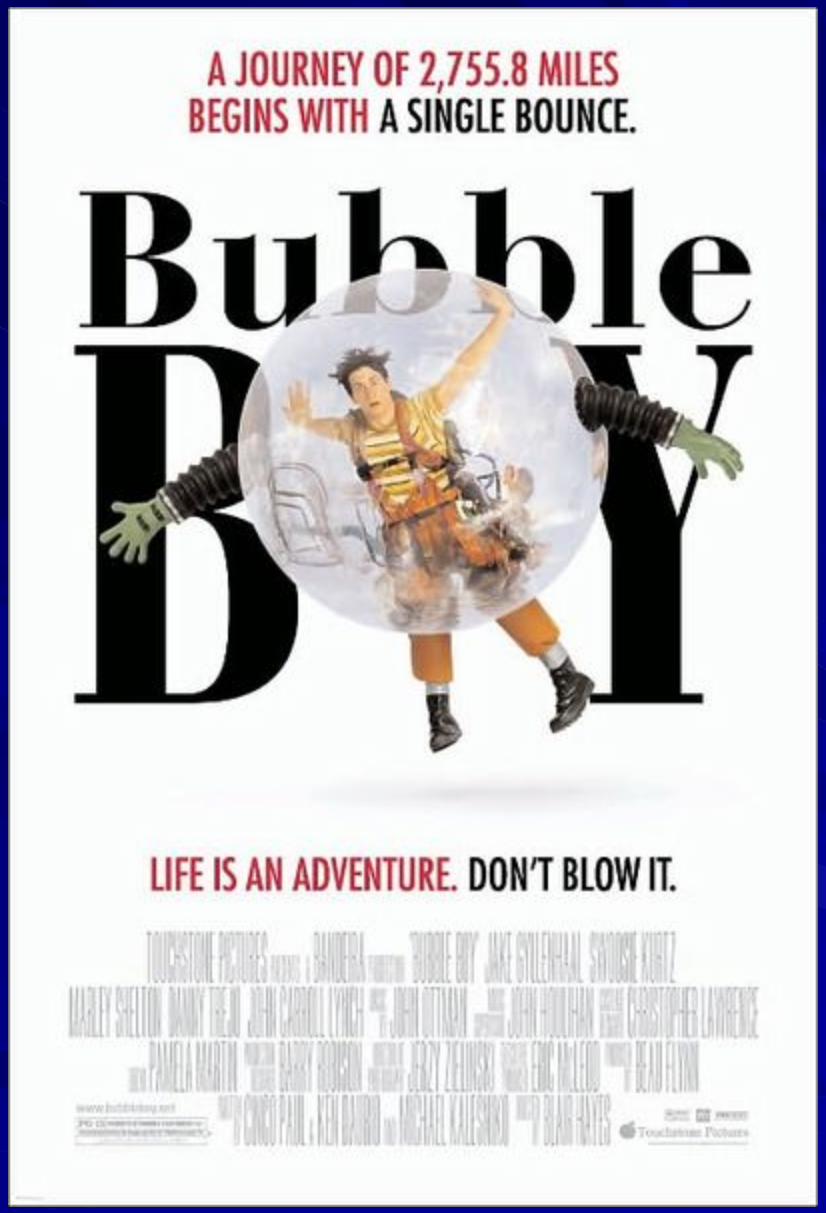
So what is a typical orphan drug?

And all human pathology is targeted by designated orphan drugs*



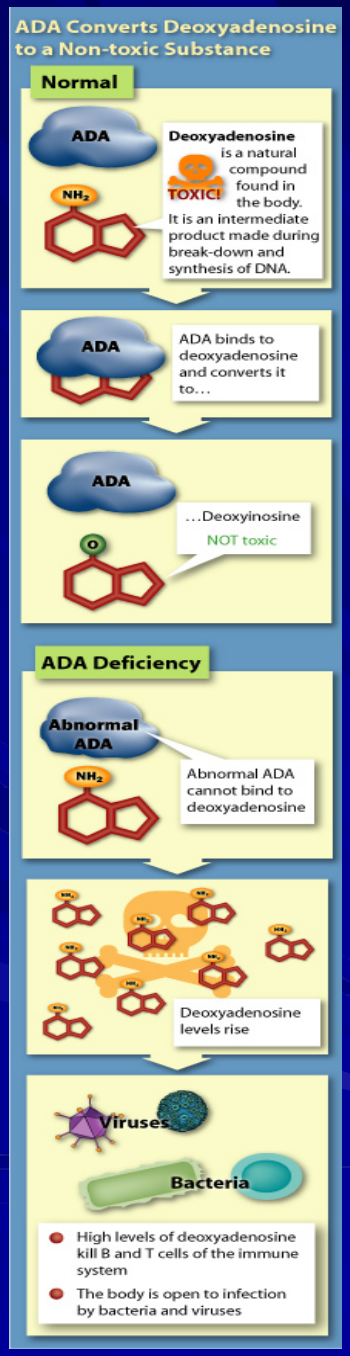
- Oncologic
- Metabolic
- Hematologic-immunologic
- Neurologic
- Infectious/parasitic
- Cardiovascular
- Transplantation
- Gastrointestinal
- Respiratory
- Endocrinologic
- Dermatologic
- Ophthalmic
- Musculoskeletal
- Injury/poisoning
- Perinatal
- Congenital abnormalities
- Others

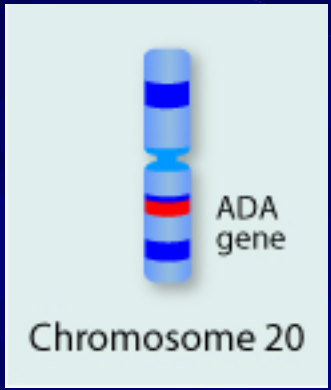
* 2000-2006 Data

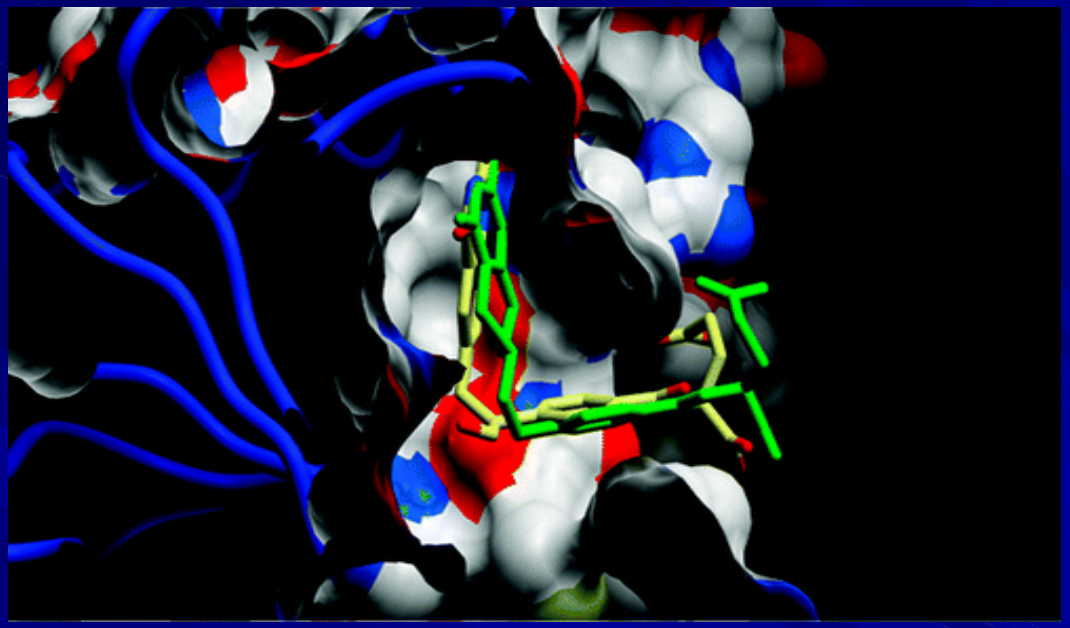

A JOURNEY OF 2,755.8 MILES
BEGINS WITH A SINGLE BOUNCE.
Bubble
Boy
LIFE IS AN ADVENTURE. DON'T BLOW IT.

Example: Adagen for ADA

- Population: $1:2x10^5$ to $1:1x10^6$ born with homozygous mutation.
- Causes Severe Combined Immunodeficiency
- Adagen is one of the first orphan drugs (based on n=12!); enzyme replacement therapy. Designated in 1984.




ADA
gene
Chromosome 20



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◄ Previous Volume 360:447-458 January 29, 2009 Number 5 Next ►

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzza, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Brigida, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Slavin, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alina Ferster, M.D., Andrea Duppenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

ABSTRACT

Background We investigated the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) due to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

Methods We infused autologous CD34+ bone marrow cells transduced with a retroviral vector containing the *ADA* gene into 10 children with SCID due to ADA deficiency who lacked an HLA-

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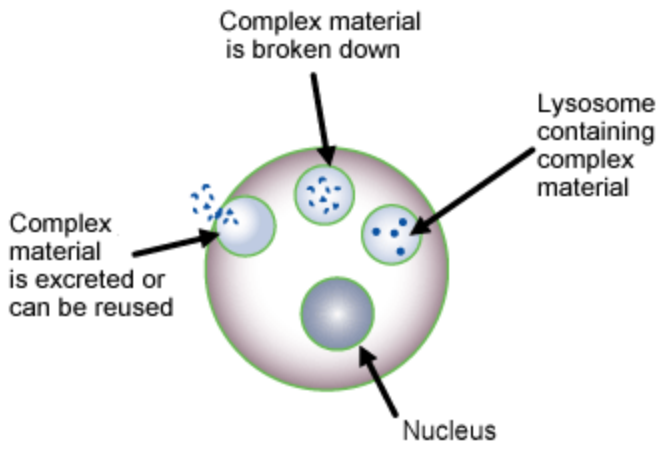
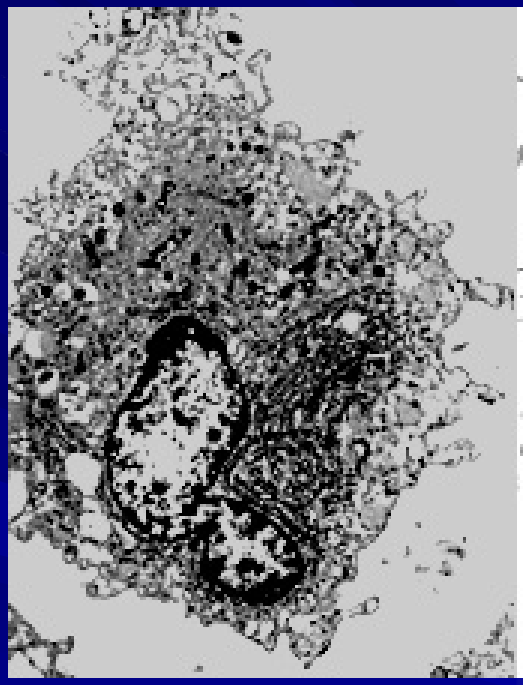
Naglazyme for MS Type VI (Maroteaux-Lamy syndrome)

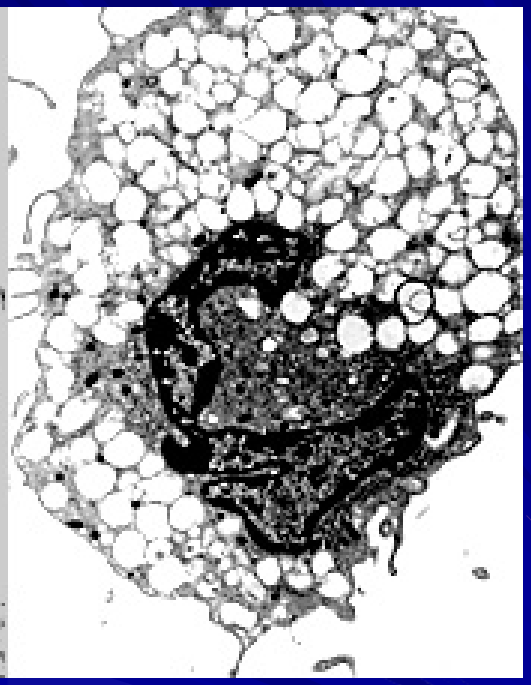
- Mucopolysacharridosis, liposomal storage disorder.
- Estimated only 1,100 persons world-wide.
- Enzyme replacement can prevent these changes

Lysosomes—Intracellular Organelles

These membrane-bound structures contain numerous hydrolytic enzymes responsible for degrading a variety of cellular components, including polysaccharides, polypeptides, lipid-linked glycosyl groups, and damaged organelles.







Enzyme Replacement Therapies

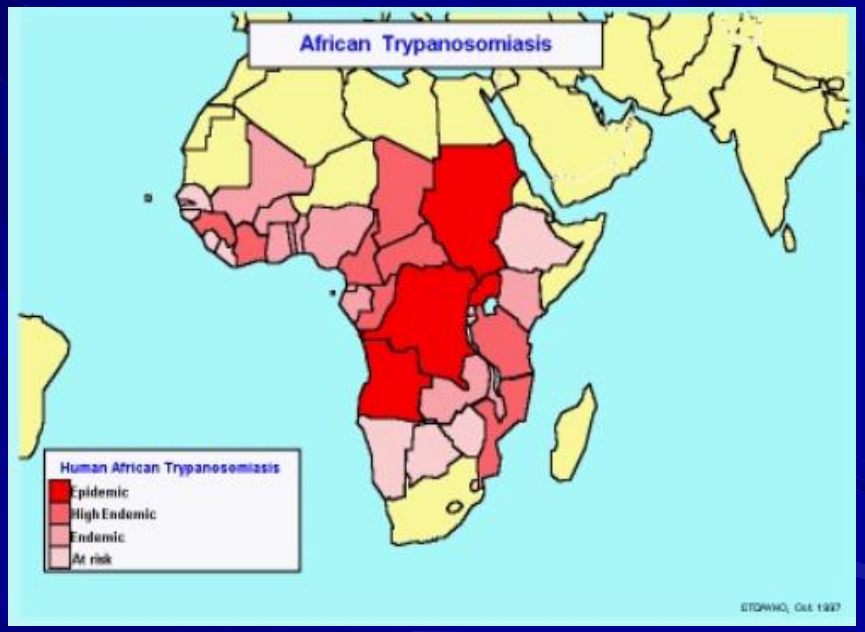
- Some of the most extraordinarily expensive treatments in the history of mankind (some ≈ $400,000/pt/yr).
- FDA does not regulate price.
- Radically transformative beneficial to patients lives.
- Exclusivity lasts 7 years; knowledge is eternal.

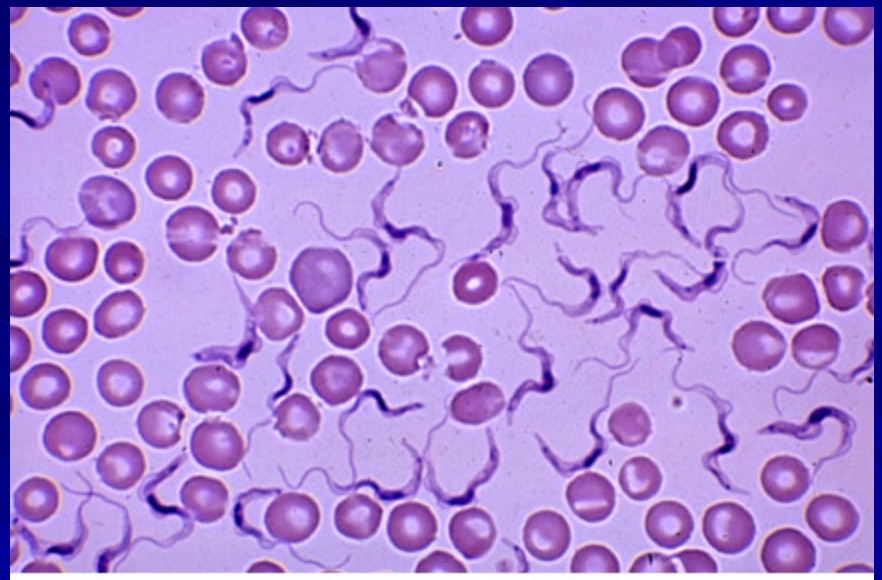
ExPTPA and Radiogardase for Radiologic Poisonings

- Two approved therapies for heavy metal poisoning, designated as orphans in 2003, 2004.
- Chelation for highly-specific indications; current zero prevalence.

Example: Eflornithine for African sleeping sickness

- Extremely rare disease in the US and Europe
- Treatment would be highly personalized, based on travel history





Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

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So what is the Orphan Designation All about?

- Non-exclusive orphan indication/moiety dyad
- Regulatory incubator of tenuous ideas.
- Target of venture capitalization
- Not a prescribe-able product
- A starting point for communication

Basis for Designation

- **First/Foremost:** What is the disease?
- **Medical Rationale Criteria**: Is there "promise" that your drug will treat it?
- **Prevalence Criteria:** Is the disease rare?

What is the disease/condition?

- First question we ask…
- Example: appetite suppressant proposed for treating Prader-Willi disease.
- Example: Adenoma regressing drug proposed for use in FAP
- Sometimes this changes/improves
  - Example: Lymphomas

Medical Rational Criteria

Must demonstrate that there is “promise” that the drug will be effective in treating said disease. “Promise” is liberally interpreted to include—

- Data from clinical trials OR
- Data from case studies/reports OR
- Data from animal models OR (rarely)
- Data from in vitro experiments
- (Note: these are data, not theories)

Prevalence Criteria

- A prevalence CAN be found for each disease.
- This is an epidemiologic question.
- Consider all published estimates. Those on best epidemiologic grounds have preference.
- Extrapolate when necessary.
- MUST be a number, not “<200,000”.
- When a range exists, we take the highest.
- Expert opinions are a last-resort option.

Test of a Medically Relevant Subset

The drug would be expected to treat only the subset of disease and NOT the rest of the disease.

Sub-setting: Truth or Dare

- NO to salami slicing
- YES to “medically relevant subsets”.
- Example: A drug to treat hypertension among left-handed people—NO.
- Example: A drug to treat renal cell carcinoma among those refractory to 1st line treatment---NO.
- Example: A drug (monoclonal Ab) against a surface antigen found in only a rare subset of breast cancer cases---YES.
- Example: A drug to be used only for stage IIb-IV melanoma---YES.
- Example---Pediatric Crohn’s Disease---YES

Rare Disease Grant Opportunities

- FDA OPD Grant Program (R01) - clinical development of products, including drugs, biologics, medical devices, or medical foods, for use in rare diseases.
- OOPD is interested in the potential of Pharmacometric analyses to support rare disease clinical trial designs and/or to evaluate clinical trial data.
- Pharmacometric studies associated with a current clinical trial would be eligible for this request for applications (RFA).
- We encourage collaboration with pharmacometricians to incorporate pharmacometric analyses.
- For more information visit the OPD Grant Program website: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/default.htm

OPD Grants Program: Budget

- The current annual budget for grant funding is approximately $14 million.
  - Clinical trials may be awarded (in total costs (direct and indirect)) :
    - Up to $200,000 (Phase 1) per year for up to 3 years

    or

    - Up to $400,000 (Phase 2 and 3) per year for up to 4 years.

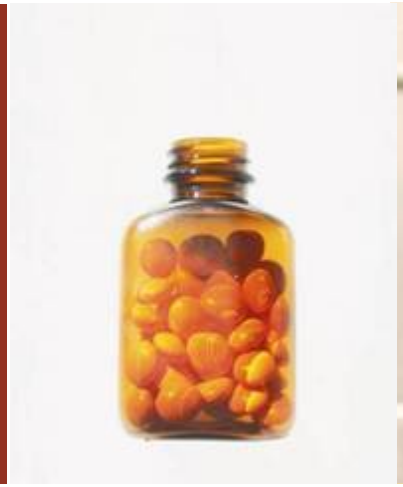
Overview Timeline FY 2012/2013 Grant Program

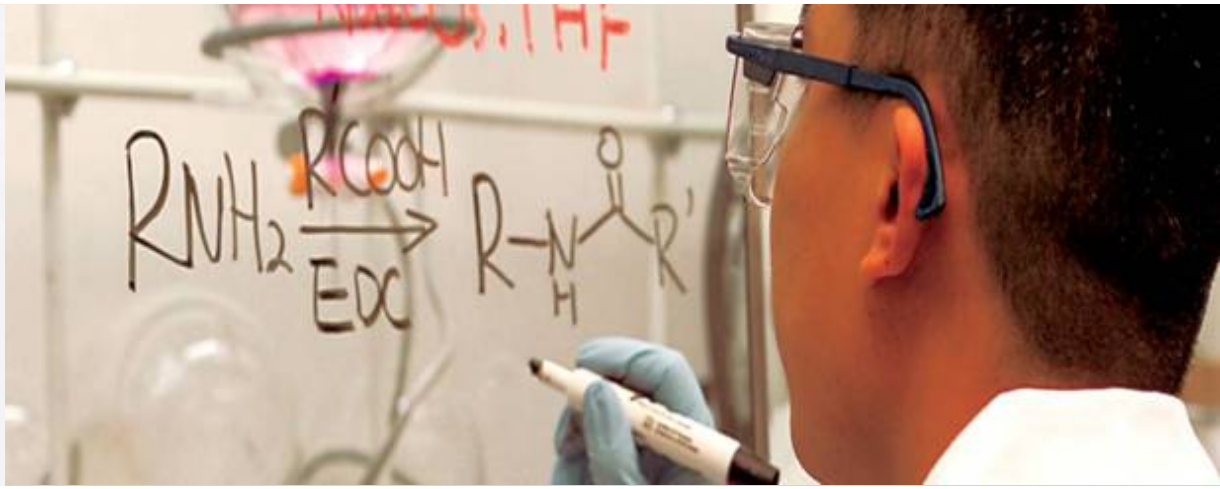
- Receipt dates:
  - Next Full Application receipt date (FY2013) - **February 1, 2012**
  - Resubmission receipt dates: **October 14, 2011 & October 15, 2012**
- **IND/IDE <u>must</u> be <u>in effect</u> at time of the grant application submission (IND must be <u>active</u> and include the protocol for which funding is requested)**
- Earliest start date for award - November 2012
- All FY 2013 funding completed by September 2013

Roles: OOPD v Review Divisions

OOPD	Review Divisions
“Promise”	Safety and Efficacy
Bragging rights	Marketing rights
Cheerleaders/advocates	Monks/dispassionate
Guests @ pre-IND/EOP2 mtgs,etc	Own pre-IND/EOP2, etc mtgs
Prevalence	Prev Irrelevant
Share shortage issues	Share shortage issues

Questions?





A Paradox in Orphan Drug Development

Trevor Mundel, M.D., Ph.D

Global Head of Development

Novartis Pharma AG

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This document represents proposals for discussion by Management. Strategies/Concepts/Projects described herein may need significant modifications before implementation, and no project should be considered final until it has been fully approved by the appropriate Novartis review process. Novartis will only implement programs that are fully consistent with all applicable laws and regulations as well as Novartis companies' policies. Before local implementation, you must ensure compliance with all applicable laws and regulations, including local industry codes, as well as local Novartis companies' policies.

The Paradox to explain

At Novartis we do not have a specific rare or orphan disease indication strategy

and yet

We spend more time and resources on Orphan/ rare disease indications than others in the industry

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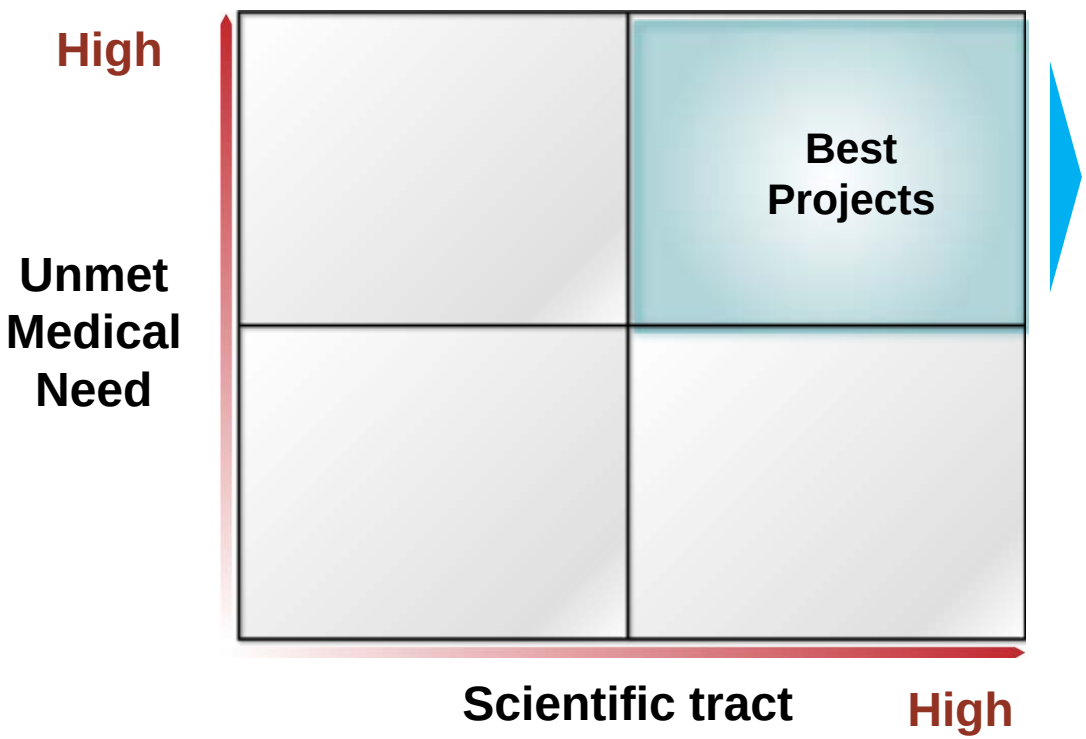
Our Approach: Focusing on Greatest Patient Need and Scientific Promise



- Diseases of high morbidity/mortality without good treatments
- Mechanism is well understood. Human genetic insights available

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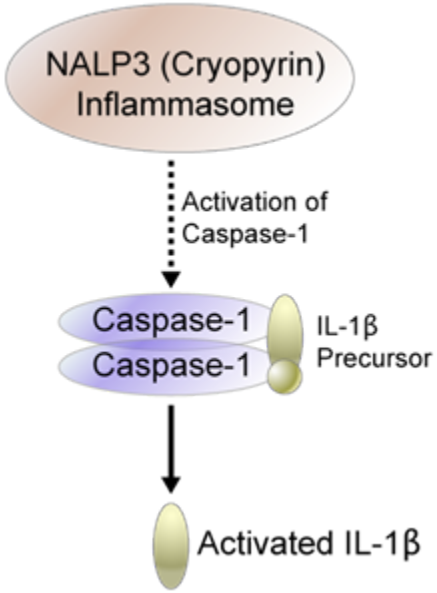
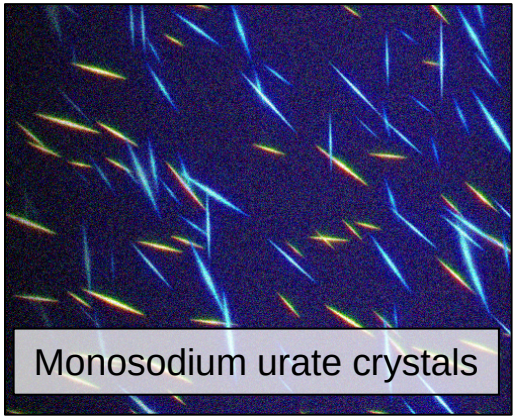
ACZ885: Anti-IL-1 β antibody

Proof of Concept in Homogeneous Population followed by Mechanistic Expansion

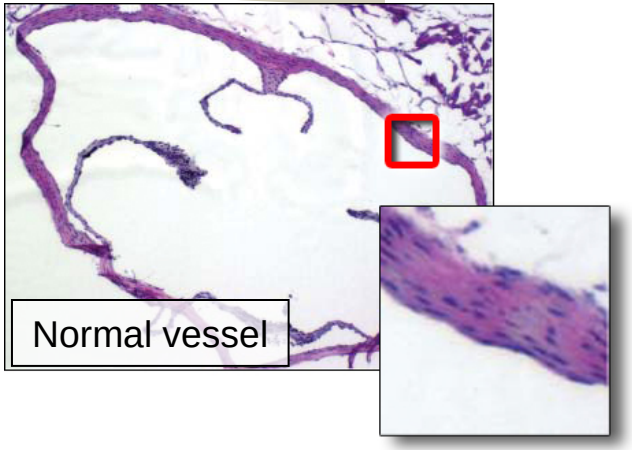
CAPS[1]
<0.020 Million

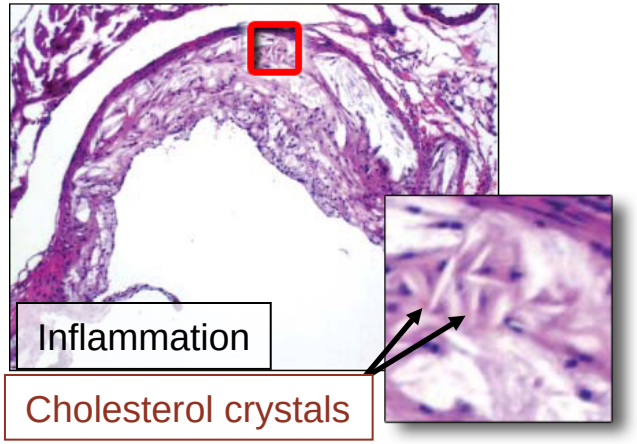


Gout
20 Million



Atherosclerosis
130 Million





Latz, et al., Nature, Vol 464|29 April 2010

[1]- Cryopyrin-associated periodic *syndrome*
Source for patient numbers: global prevalence estimate from Patient Base

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SJIA patients are aged <16 years and show distinctive extra-articular disease features

Osteoporosis in juvenile idiopathic arthritis

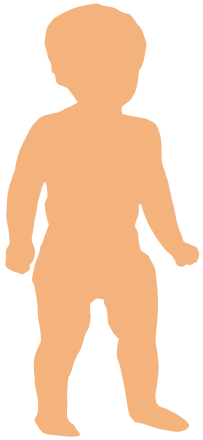
Woo P (2006) Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome
Nat Clin Pract Rheumatol **2:** 28–34 doi:10.1038/ncprheum0084

Arthritis (usually polyarticular)[1]

Peak age of onset 18 months–2 years[1]

Spiking fever (39°C or higher)[1]

Distinctive erythematous skin rash[2]



Growth retardation[2]

Distinctive joint disease[3]

1. Frosch M, *et al*. *Rheumatology* 2008;47:121–125; 2. Woo P. *Nat Clin Pract Rheumatol*. 2006;2:28–34; 4. Coombes A, *et al*. *Eye* 2003;17:258–260.

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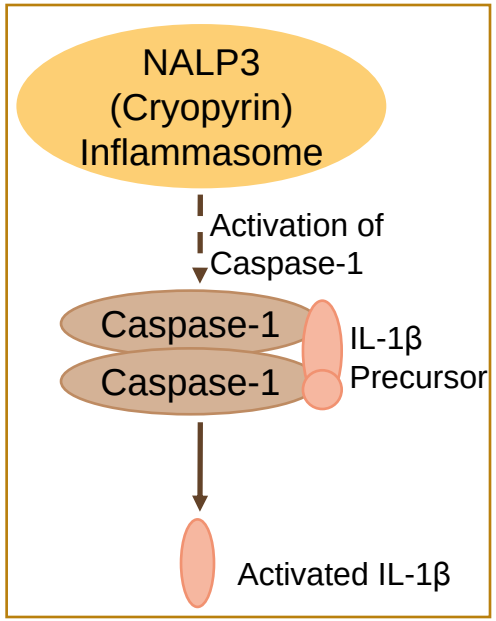
ACZ885 – Mechanistic indication expansion



COPD[1]
Phase II

Osteoarthritis
Phase II

CV Risk
reduction
Phase II

Refractory
Gout
Phase III
(On track for Q4
2010 submission)

SJIA[2]
Phase III

CAPS[3]
Marketed

[1] *Chronic Obstructive Pulmonary Disease*
[2] *Systemic juvenile idiopathic arthritis*
[3] *Cryopyrin associated periodic syndrome*

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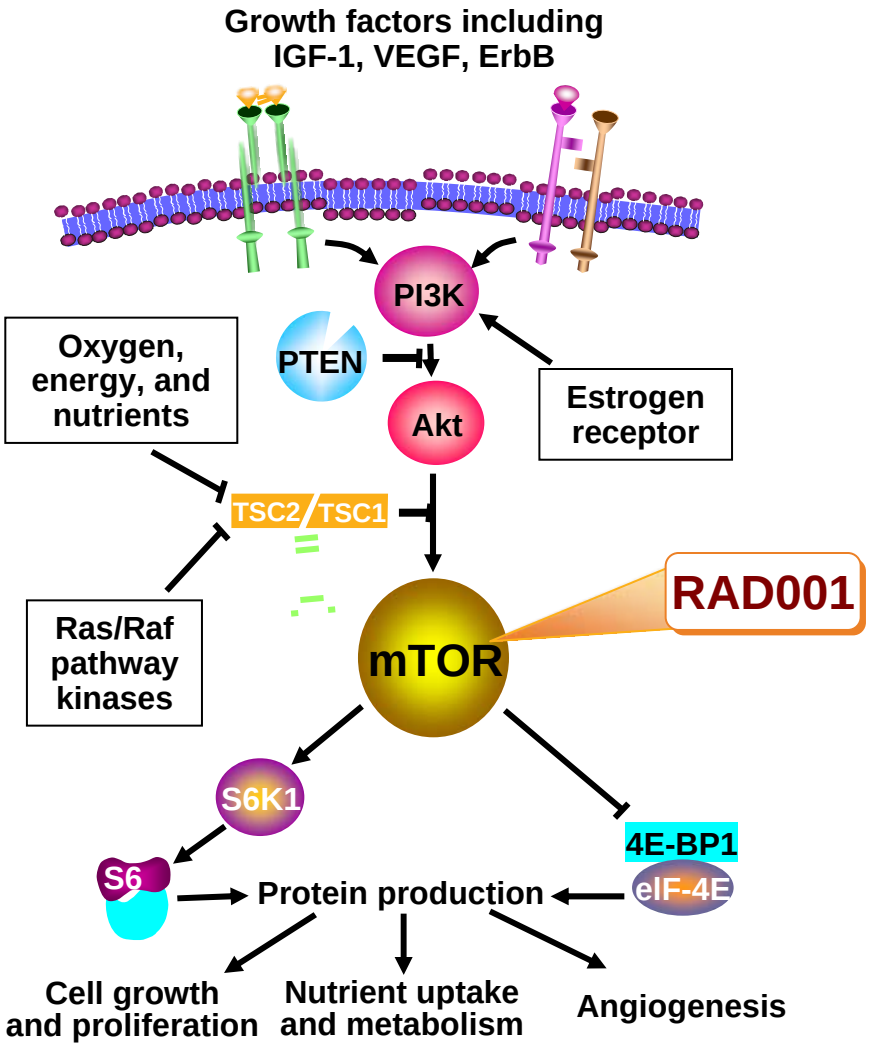
The mTOR Pathway Is Activated in Tuberous Sclerosis – targeted by Everolimus



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Tuberous Sclerosis: A rare Autosomal Dominant Genetic Disease

Skin lesions including facial angiofibromas in >90% of patients

Krueger and Franz. *Pediatr Drugs*. 2008;10:299-313

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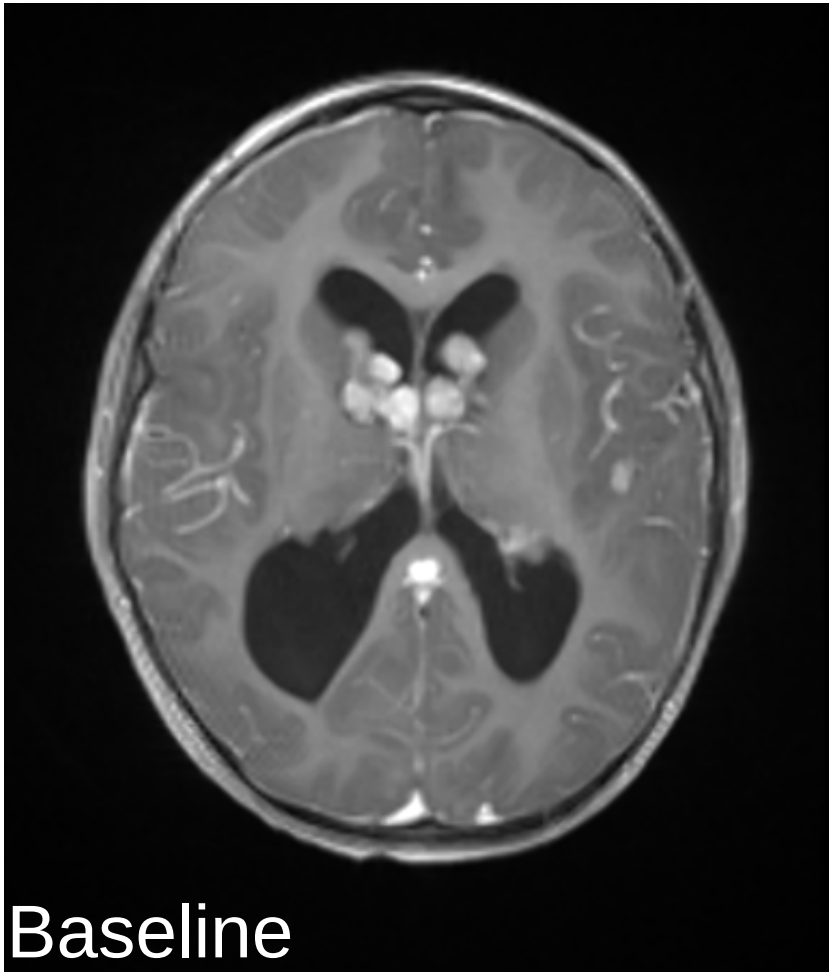
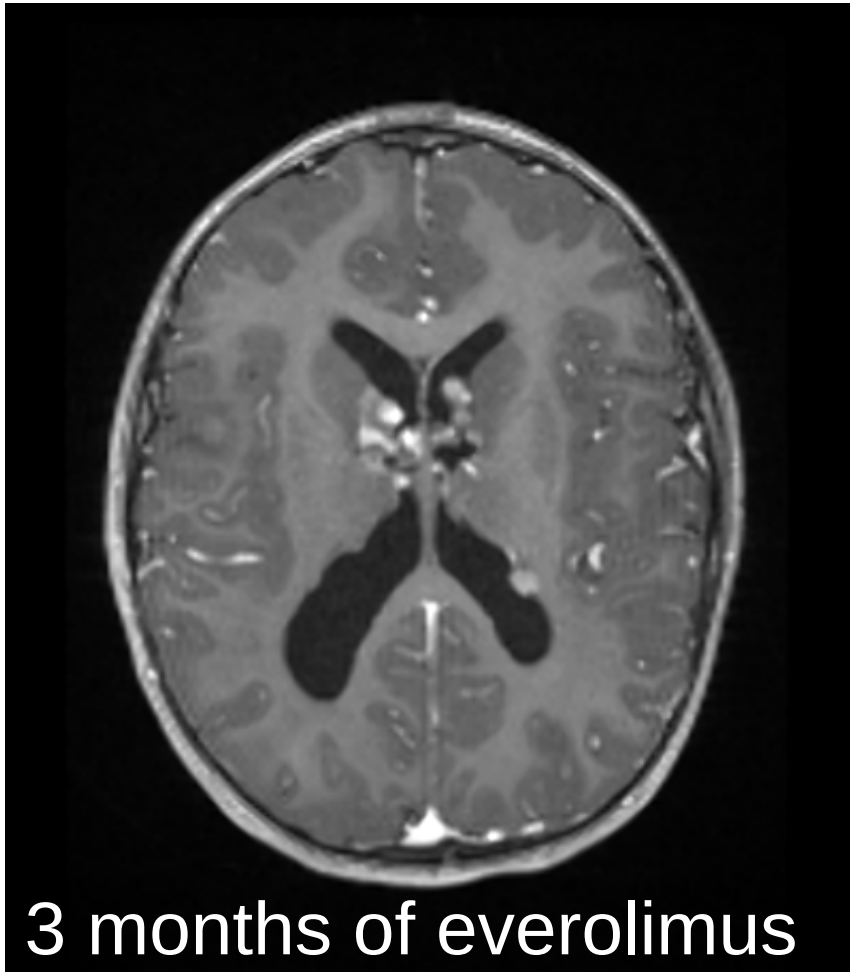
SEGA Volume Response and Resolution of Hydrocephalus





Franz DN. *N Engl J Med*. 2010. In Press.

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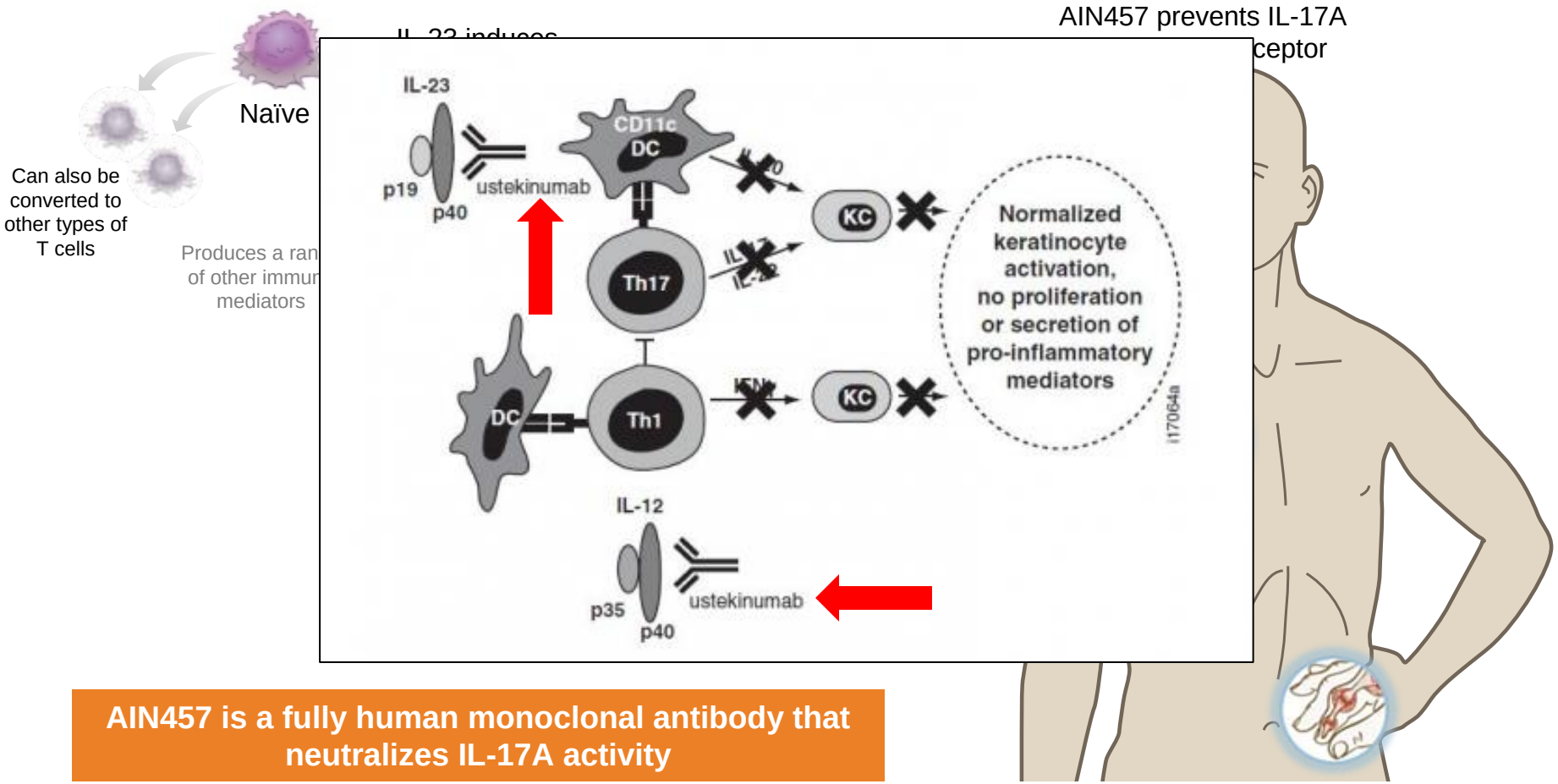
AIN457 (secukinumab) Potential to be first-in-class in immune mediated diseases

IL–17A, a key product of Th17 cells, plays an important role in the pathogenesis of immune diseases such as psoriasis, and rheumatoid arthritis



AIN457 is a fully human monoclonal antibody that neutralizes IL-17A activity

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AIN457 – proof in psoriasis

Baseline

After 2 weeks of treatment

After 4 weeks of treatment

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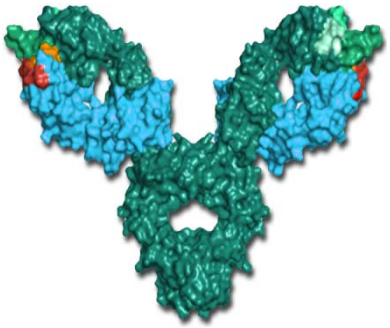
AIN457 – Parallel indication expansion



Crohn's Disease
In PoC trial[1]

Multiple Sclerosis
In PoC trial[1]

Psoriatic Arthritis
Phase II

Ankylosing spondylitis
Phase II

Psoriasis (Moderate to severe)
Phase II

Rheumatoid arthritis
Phase II

Note: Non-infectious uveitis in patients with Behcet's disease did not meet its primary endpoint and the data did not support submission of AIN457 for this indication
Other uveitis studies are continuing.

[1] *Proof of Concept not yet established*

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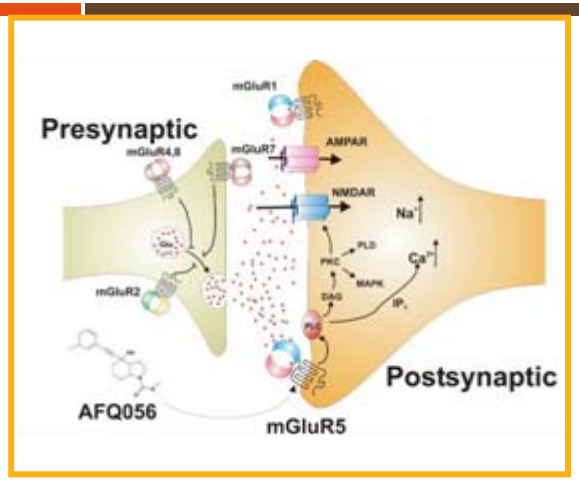
Three indications being pursued based on AFQ056's inhibition of hyperglutamergic transmission



AFQ056 MoA[2]

Huntington's Disease

- in PoC trial[1]

Fragile X Syndrome

- Phase II

Parkinson's Disease L-dopa-induced dyskinesia

- Phase II

[1] *Proof of Concept not yet established*
[2] *Mode of Action*

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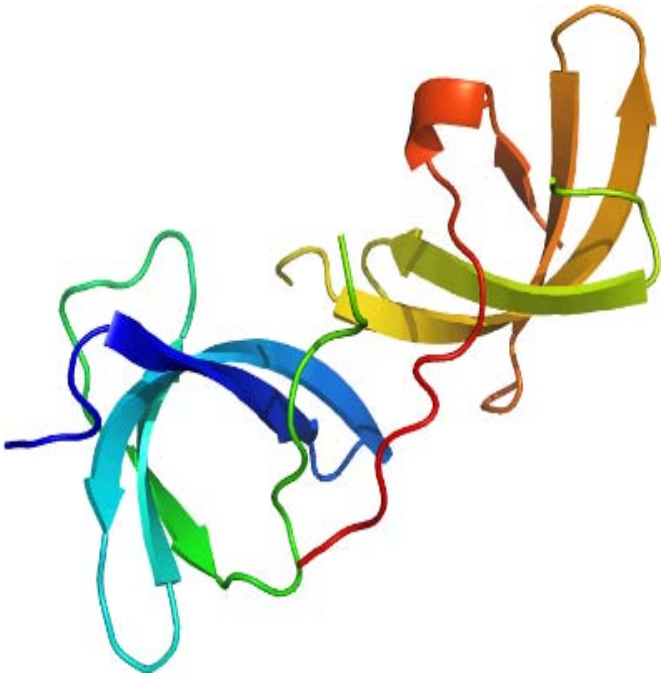
Driving patient outcomes through focused solutions & interventions

AFQ056 FXS

- Potential for AFQ056 to be first targeted Fragile X Syndrome therapy
- Difficult diagnostic - quantitatively measuring small differences in a DNA modification to predict response. No existing test
- Biomarker Development Group (BMD) and MDx have developed a novel platform and validated test that is ready for clinical trials and FDA submission
- Opportunity for long term clinical-diagnostic approach spanning prenatal, neonatal, pediatric, adolescent and adults



Source: Amaya MF, Adams-Cioaba MA, Guo Y, MacKenzie F, Kozieradzki I, Edwards AM, Arrowsmith CH, Bochkarev A, Min J.; http://www.thesgc.org/structures/structure_description/3H8Z/

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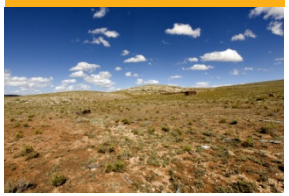
Issues & Conclusion

Ethics

- Continuation of prescription for responders if few and no extension

Geography



- Sparse patient population spread across vast geographies/countries, with varying constraints

Incentive

- Regulatory & market incentive must be significant to overcome barriers to innovation

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A Clinical Pharmacology Decision Tree for Orphan Drugs

CAPT E. Dennis Bashaw, Pharm.D.
Dir. Division of Clinical Pharmacology-3
Office of Clinical Pharmacology
US Food and Drug Administration

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.

The Orphan Drug Act
Jan. 4th, 1983

- While the ODA does *NOT* comment on the issue of informational needs or reviewing standards, it does provide incentives for the developer, including:
  - 7-year market exclusivity provision granted for FDA-designated orphan drug indications
  - a 50% tax credit for expenditures incurred during the clinical testing phase
  - Grants available to pursue development
  - Fee Waivers

Informational Considerations

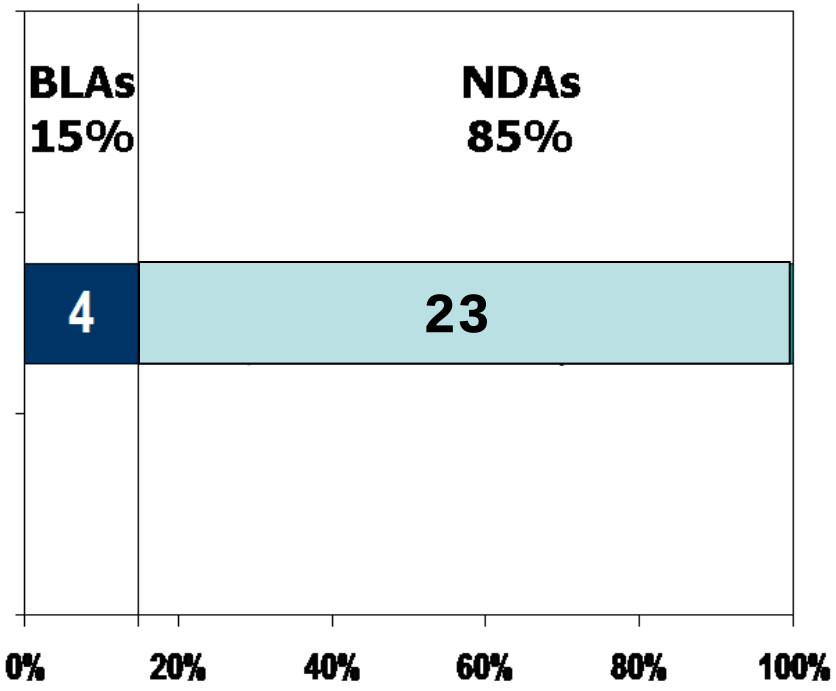
- New Molecular Entity vs. Repurposed Drug
- Population Size Affected
  - <200,000-10,000 Juvenile Rheumatoid Arthritis (150,000)
  - <10,000-1,000 Pompe Disease (7,300)
  - <1,000 N-acetylglutamate Synthase Deficiency (<200?)
- Ability to use healthy subject data
  - Toxicity
- Special Populations

1983-2006 & Clinical Pharmacology

- In 1983 the state of the art of Clinical Pharmacology was very rudimentary
  - Pharmacokinetics was only required for an NDA filed after July 4th 1977.
  - In 1987, the Division of Biopharmaceutics had a total of 5 IBM PC-XTs
  - Handwritten draft reviews were the norm.

Original Orphan Approvals (1983-1987)*

- 27 Orphan Approvals
  - 4 BLAs
  - 23 NDAs
- First Orphan Drug Approved
  - (7/20/83)Hemin for acute intermittent porphyia
- Approval Clock did not allow for Priority or Standard Review timelines.



*1/4/1983-12/31/1987

Computing 2011

- In 2011, while paper NDA submissions are still submitted, more and more data comes to the FDA in an electronic format for review.
- The FDA has continued to upgrade its computer resources including the Computational Science Center whose mission is
  - *To support CDER in continually improving the optimal drug evaluation and review process for the entire drug lifecycle while addressing the dynamic nature of the healthcare system*

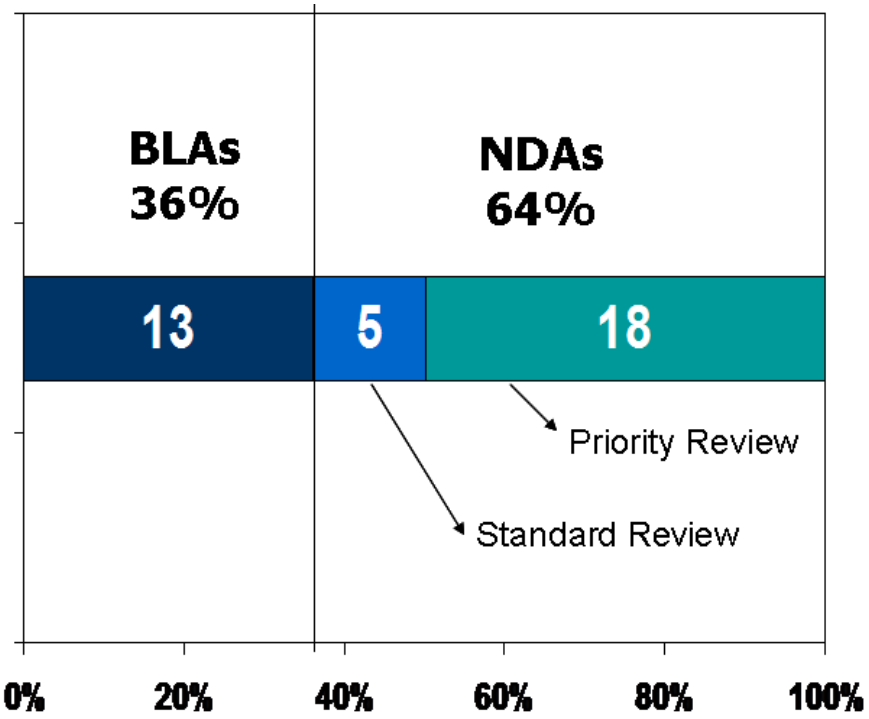
CDER Computational Science Center

Center for Drug Evaluation and Research
CSC
Computational Science Center

Better Data, Better Tools, Better Decisions

Recent Approvals (2006-2010)*

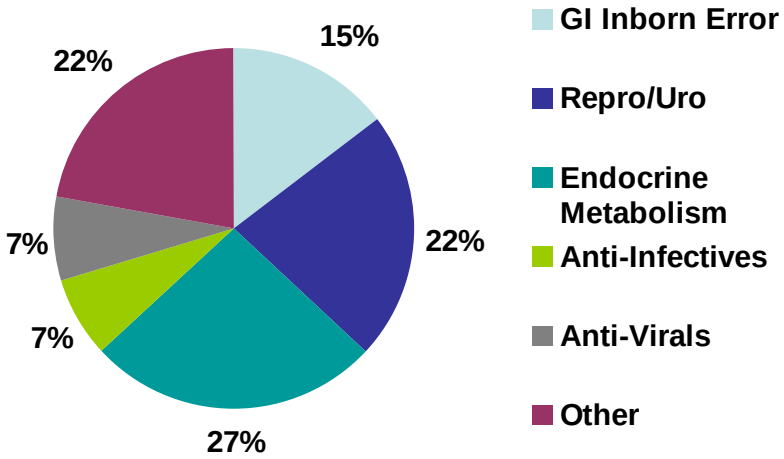
- 36 Approvals
  - 13 BLAs
  - 23 NDAs
- The 36 approvals represent 30 separate indications, 6 indications had 2 approvals
- These represent 29 different companies, both Novartis and Genzyme had 3 approvals each in this period.



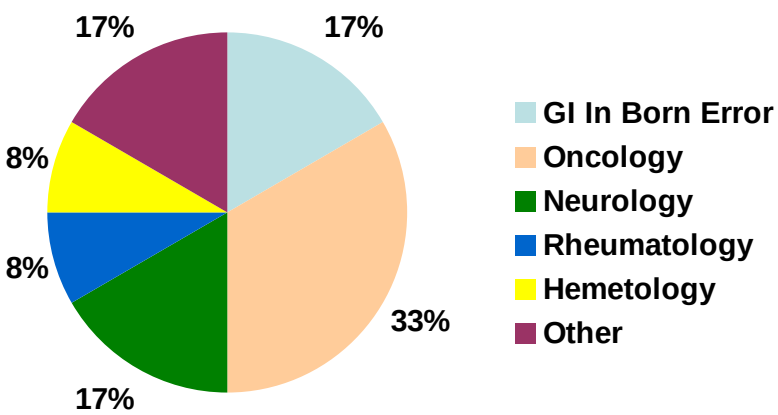
*1/1/2006-12/31/2010

Therapeutic Areas Over Time

1/1/1983-1/1/1988*



1/1/2006-1/1/2011



*Categories as of 2011

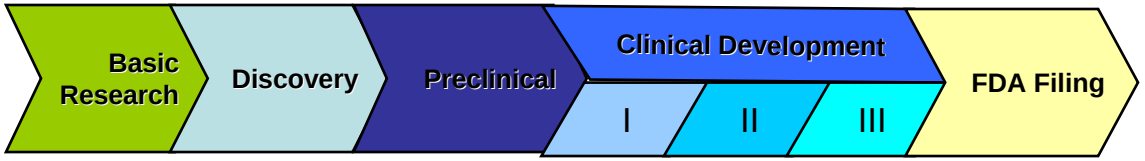
Informational Content of Orphan/Rare NDAs/BLAs 2006-2010

	N	Radio-labeled	Single Dose	Multiple Dose	DDI	QT	Renal	Hepatic	PopPK	Other*	Total
NDA (P)	**18**	**9**	**40**	**37**	**12**	**4**	**4**	**4**	**26**	**172**	**326**
NDA (S)	**5**	**2**	**15**	**12**	**8**	**3**	**2**	**2**	**11**	**54**	**114**
BLA	**13**		**16**	**28**			**1**		**5**	**14**	**77**
Totals	**36**	**11**	**71**	**77**	**20**	**7**	**7**	**6**	**42**	**240**	**517**

*includes, analytical reports, literature articles, animal data, protein binding, In vitro CYP450 studies, etc.

Decision Tree As A Strawman Proposal

- Presented to stimulate discussion-Not as a lockstep roadmap
- To challenge assumptions
- To propose a pathway for rational drug development that makes use of existing paradigms.



Developmental Paradigms

Pediatric

- Using data from adult subjects to define metabolism, dose response, drug interactions and allowing us to focus on the pediatric aspects.

Oncologic

- Using a combination of small numbers of patients with appropriate use of animal and other collateral data along with pharmacometric tools to assess dose/concentration response features.

Developmental Paradigms (cont'd)

Re-purposing

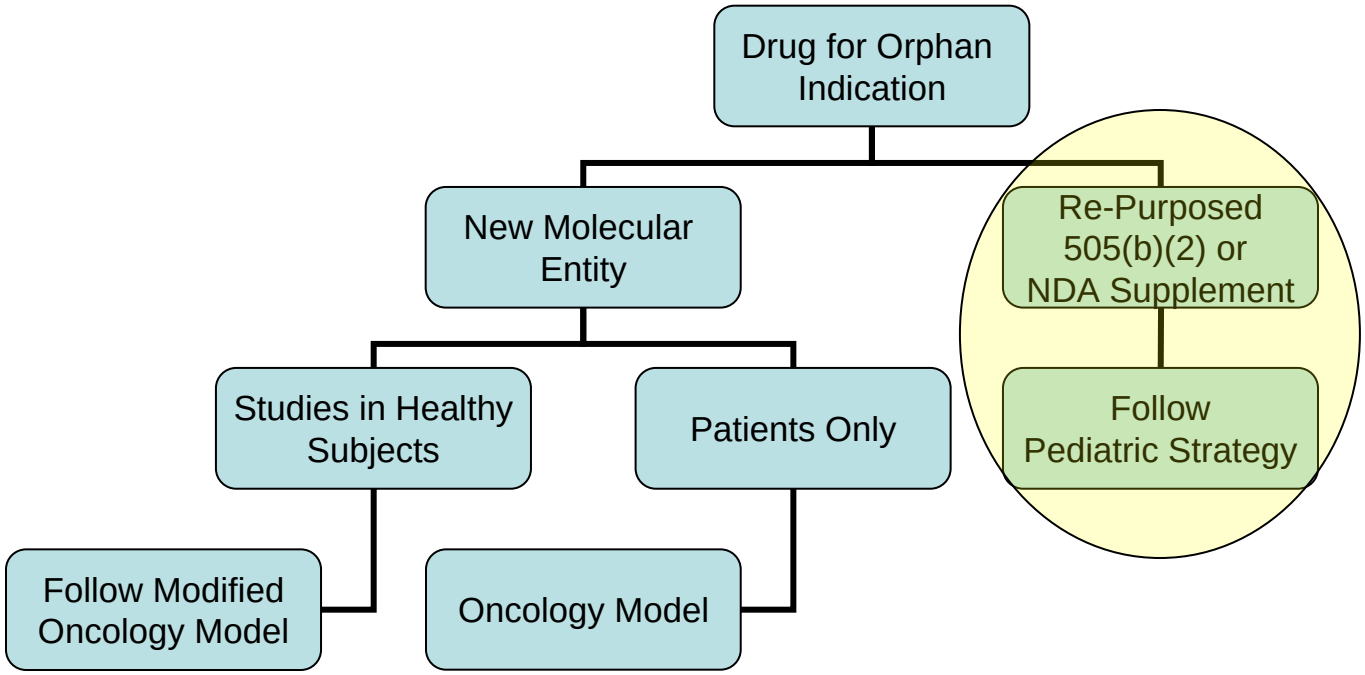
- As used in this discussion is the development of an already approved drug for use in an orphan indication.
- The use of knowledge of related disease/drug mechanisms to identify potential drug candidates at any stage of development
- Generally allows the fastest route for a drug as the initial mass-balance, animal safety, drug interaction, and special population work is already done.
- Development program is targeted to the orphan populations needs in terms of dose and any potential intrinsic factors that may affect drug disposition.

Rare Disease Repurposing Database (RDRD)-*BETA Version*

- The Office of Orphan Products Development (OOPD) has established a new resource for drug developers-a database of products that:
  - have received orphan status designation (i.e. they've been found "promising" for treating a rare disease)
  - are already market-approved for the treatment of some *other* diseases.

- While the data included in the RDRD is a re-configuration/cross-indexing of already FDA-released information, it offers a new tool for finding special opportunities to develop niche therapies that are already well-advanced through development.
  - These drugs have already been subjected to pre-clinical (e.g., pharmacokinetic and toxicologic) testing and are already deemed to be pharmacologically active, effective and safe in some clinical context.

Clinical Pharmacology Decision Tree for Orphan Drugs



Pediatric Drug Development Model (Re-Purposing)

- Drug already approved for use in an Adult population
  - Basic Pharmacokinetic Properties and Clinical Pharmacology studies already conducted and can be “borrowed” to support use in pediatric patients.
- For an Orphan Disease
  - Dose response (efficacy) relationship needs to be established
  - Safety in targeted population
  - Biomarker Development and Qualification
    - Clarify Pharmacodynamics

Re-Purposing Example-Sildenafil

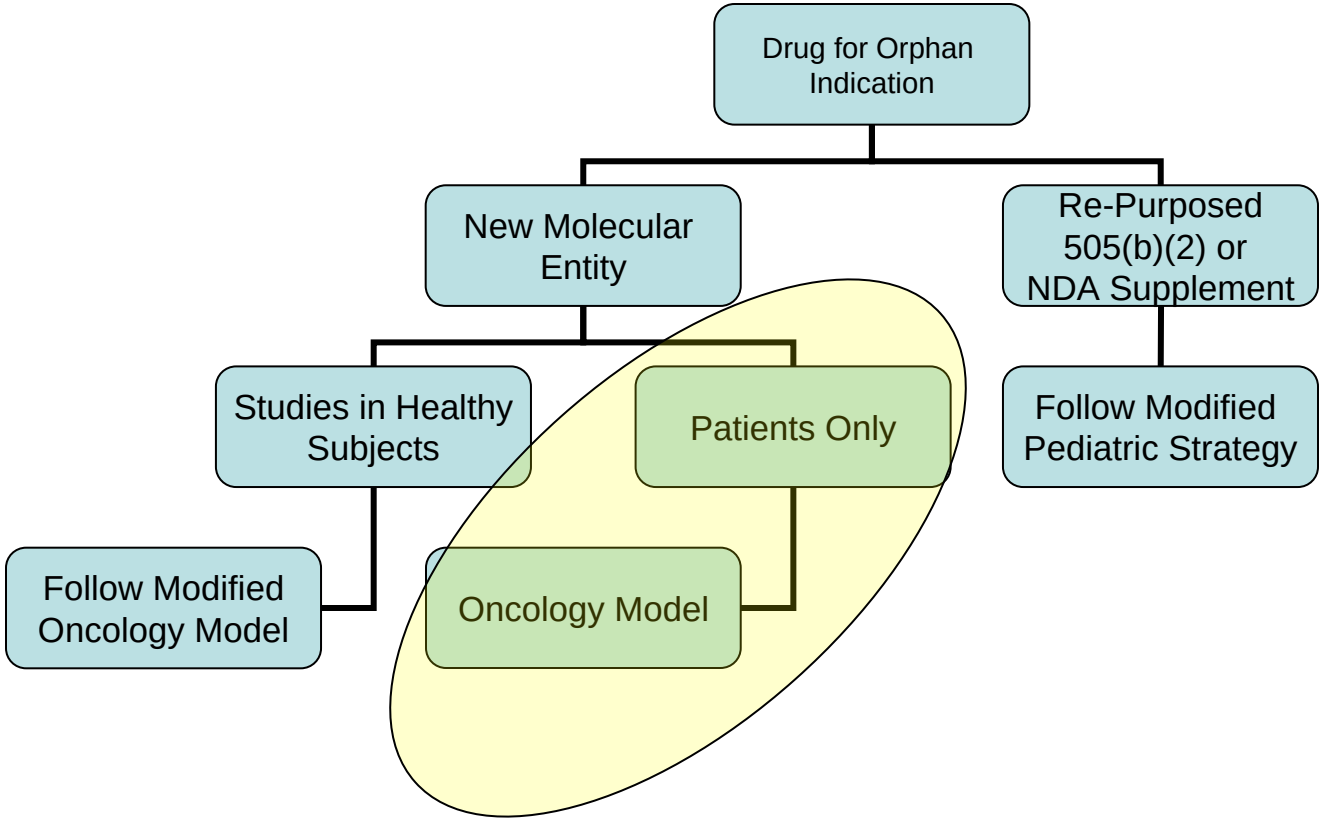
- Sildenafil is a potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), and was initially studied for use in hypertension and angina pectoris.
- It was approved in March 1998 for the "treatment of erectile dysfunction"

Clinical Pharmacology Studies	# Subjects
Pharmacokinetics	228
DDI	82
Pharmacodynamics	243
Pharmacodynamic DDI	123
Total Clinical Pharmacology Population	**676**

Re-Purposing Example-Sildenafil

- Idiopathic pulmonary arterial hypertension (PAH) is a rare disease with an incidence of about 2-3 per million per year and a prevalence of about 15 per million.
- In June 2005 sildenafil was approved under an orphan drug designation for treatment of PAH to improve exercise ability under the brand name Revatio.
- The Clinical Pharmacology section of the sNDA consisted of 15 post-marketing study reports (DDIs in non-PAH subjects), 3 new studies in PAH, and 1 DDI study (bosentan).
- A total of 230 patients with PAH were studied in the Clinical Pharmacology portion of the sNDA.

Clinical Pharmacology Decision Tree for Orphan Drugs



New Molecular Entity-Patients Only

- Oncologic Drug Development Model
  - Basic Clinical Pharmacology
    - Pre-Clinical
    - Mass Balance
    - Use of Animal Models
    - Biomarker Development
  - Characterize Pharmacokinetics in Patients With Population Based Tools
    - Special Populations Within Orphan Population
  - Prioritize Drug-Drug Interaction Studies Based on Mechanism

DRUG EXAMPLE-Carbaglu

- Carglumic acid is a structural analogue of N-acetyl-glutamate
- *N*-acetylglutamate synthase (NAGS) deficiency is the rarest disorder of the urea cycle, with only a handful of cases worldwide-a true prevalence is unknown.
- Without that enzyme, *N*-acetylglutamate does not form and activate the first enzyme of the urea cycle. The consequence is a buildup of ammonia, which can eventually cross the blood–brain barrier and cause neurologic problems, cerebral edema, coma, and death.

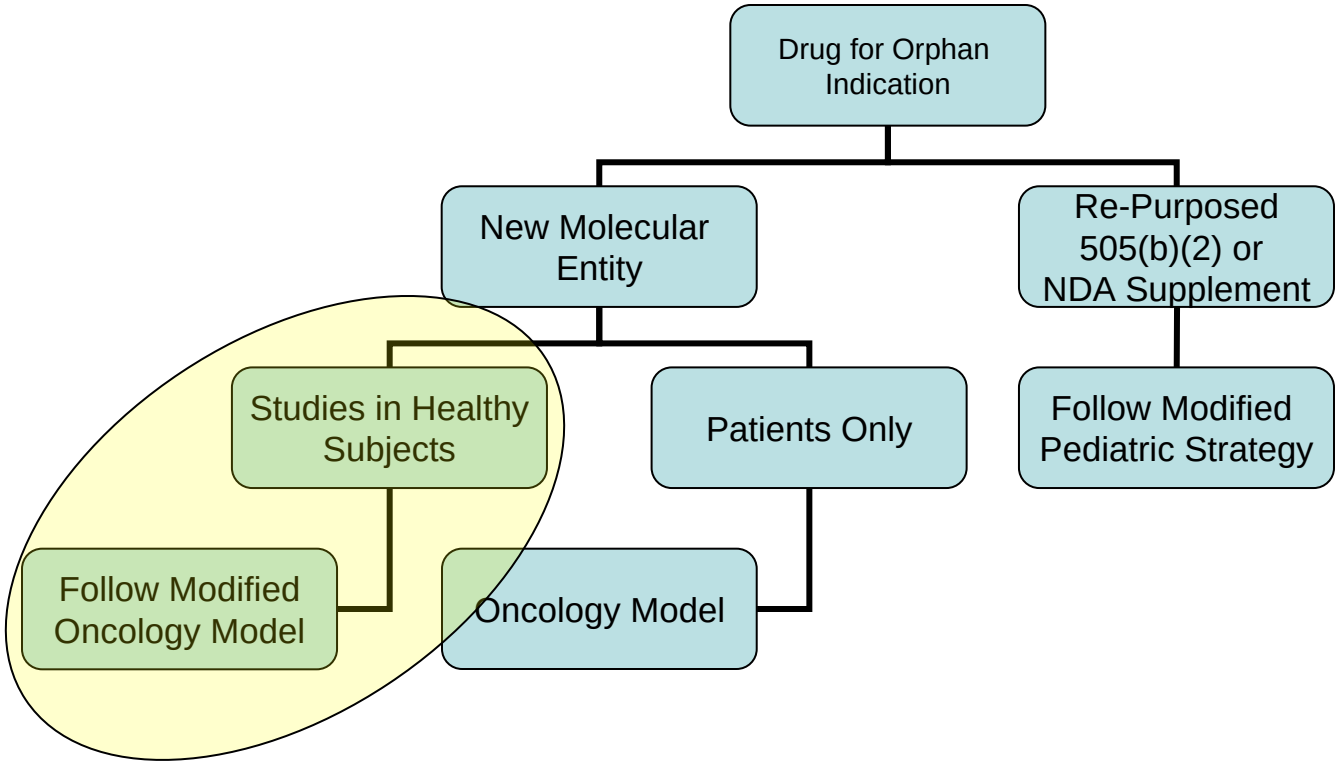
Clinical Pharmacology Studies	# Subjects
Biopharmaceutics	15
Pharmacokinetics/Pharmacodynamics	23

Carbaglu-Orphan Development Paradox

While Clinical Pharmacology studies could have been done in healthy subjects, the nature of NAGS deficiency is such that the validity of extrapolating healthy subject data to the target patient population is unknowable.

Ironically, given the small number of subjects in the entire population the number of subjects studied is actually a higher percentage of the total disease population. Thus, our understanding of the drug:disease is quite high.

Clinical Pharmacology Decision Tree for Orphan Drugs



New Molecular Entity-Healthy Subjects

- Modified Oncologic Drug Development Model
  - Basic Clinical Pharmacology
    - Pre-Clinical
    - Mass Balance
    - Biomarker Development
  - Basic Pharmacokinetic Development (SAD, MAD, etc.) Can Be Done in *Healthy* Subjects
    - Special Populations
    - Drug-Drug Interaction Studies
  - Characterize Pharmacokinetics in Patients With Population Based Tools

Drug Example- Argatroban

Argatroban is a small molecule direct thrombin inhibitor, it was approved in 2000 for the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombo-cytopenia (HIT). The prevalence of HIT is unknown.

Clinical Pharmacology Studies	# Subjects
Pharmacokinetics	33
Pharmacodynamics	54
Special Populations	81
DDI Studies	106
Cardiac Studies (angina/cardiac catherization)	19
Total Clinical Pharmacology Population	**293**

Quo Vadis?

- The ODA has had a major influence on the development of therapies for orphan and rare diseases, much more remains to be done.

- While the FDA has increased its capacity for improved data analysis since 1984, much more can be done with improved tools.

Oncologic and Pediatric Models for Orphan Drug Development

- The use of these models is not new, they have been used successfully since the earliest work in these populations.
- The purpose of the strawman proposal presented here at the Advisory Committee is to encourage a broader recognition of it in the community and to invite discussion as to how and where the informational needs can be modified without compromising patient safety.

Acknowledgements

- OCP Rare Disease Working Group
  - Larry Lesko
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  - Angela Men
  - Lei Zhang
  - Christine Le

Clinical Pharmacology Tools for Developing Drugs for Rare Diseases

Christine Garnett, Pharm.D.
Division of Pharmacometrics
Office of Clinical Pharmacology

Impact of Quantitative Pharmacology– Selected Examples

Argatroban

- Exposure-response (ER) modeling primary basis for dosing approval in pediatrics

J. Clin Pharamcol. 51:19-28, 2011

Tetrabenazine

- ER supportive evidence of effectiveness
- Basis for dosing in poor metabolizers

Clin Pharmacol Ther. 81(2):213-221, 2007

Levofloxacin

- PK matching primary basis for dosing approval in pediatrics

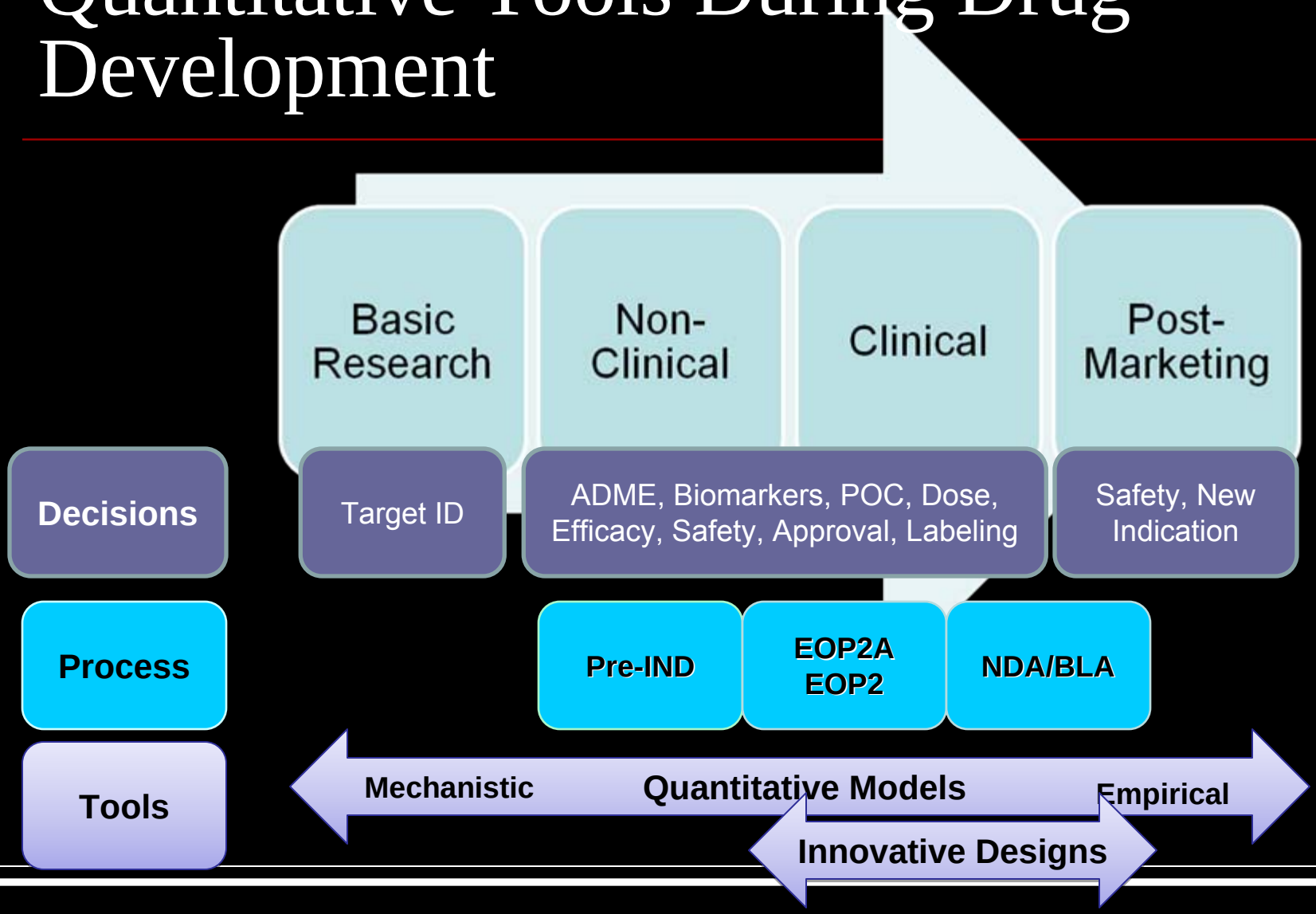
Antimicrob Agents Chemother. 54(1):375-379, 2010

Sildenafil

- PBPK modeling alleviated need for additional DDI study

Clin Pharmacol Ther. 89(2):259-267, 2011

Quantitative Tools During Drug Development



Quantitative Tools

INNOVATIVE ANALYSES

- Quantitative drug-disease-trial models
- Exposure-response models

INNOVATIVE TRIAL DESIGNS

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

KNOWLEDGE MANAGEMENT

- Leverage prior data

Innovative Analyses

- Exposure-response to support B/R and dose selection
- Disease-drug-trial models to gain insights into biomarkers and endpoints
- Prioritize drug interactions studies based on in vitro and in silico predictions (PBPK)
- PopPK approaches for intrinsic/extrinsic factors

DEVELOPMENT IMPACT

- Streamline Clin-Pharm package
- More efficient trials based on mechanistic reasoning

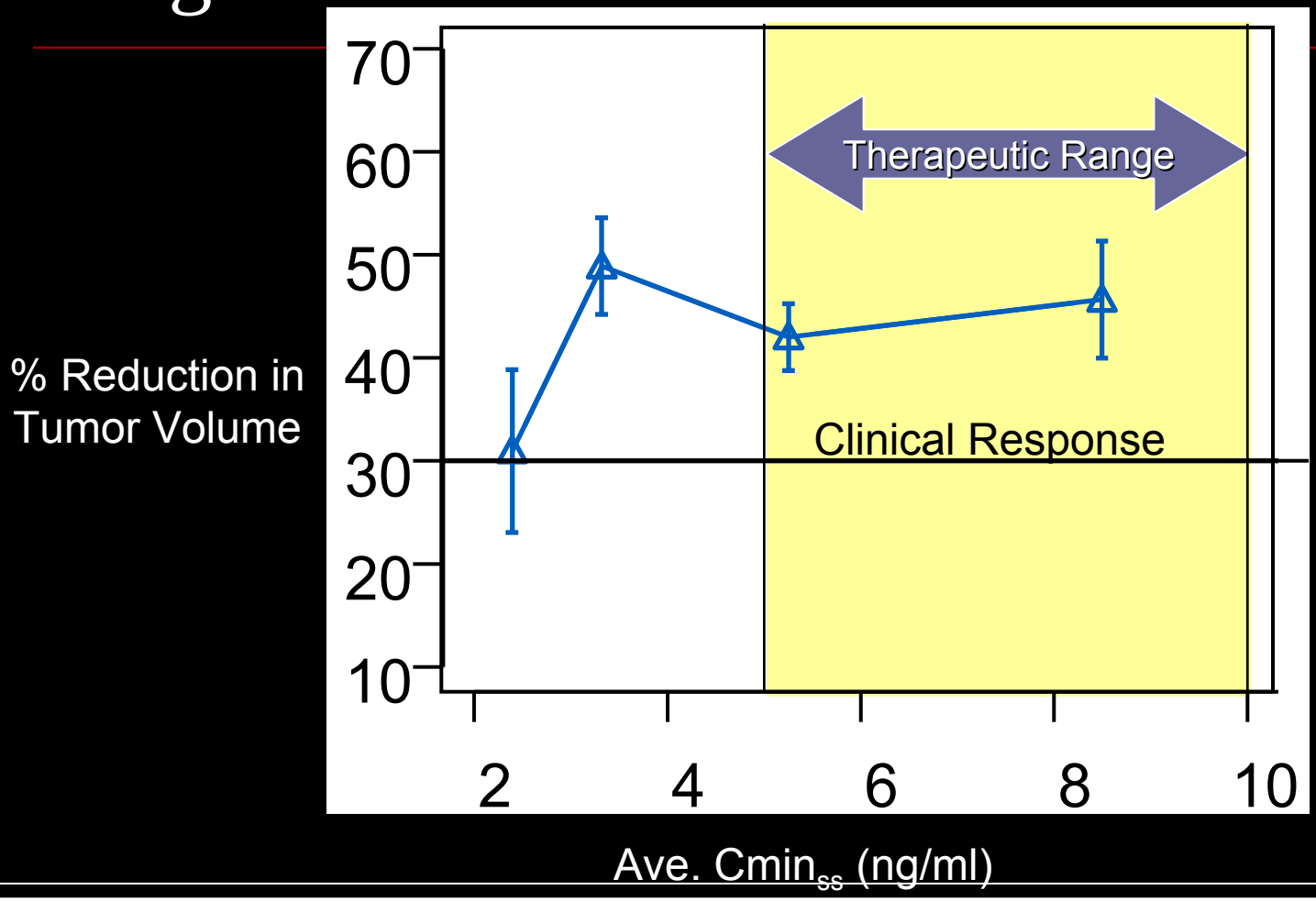
REGULATORY PATHWAY

- Guidance documents
- Critical Path modeling consortia

Everolimus for Patients with SEGA

- Re-purposed Drug
  - Approved for RCC and prophylaxis of organ rejection
- Regulatory Pathway
  - Accelerated approval based on single-arm clinical trial in 28 patients
  - No new clinical pharmacology trials
  - Dosing based on therapeutic drug monitoring
- Tool Used for Regulatory Decision
  - Exposure response analysis supported anti-tumor activity in single arm trial and target therapeutic range.

Evidence of Anti-Tumor Activity in Single-Arm Trial



Innovative Trial Design

- Enrichment
- Design
  - Crossover designs
  - Dose-response
  - Adaptive dosing and sample size
- Clinical Trial Simulation
  - Explore competing trial designs to maximize power & informativeness
  - Dose selection

DEVELOPMENT IMPACT

- Increase success rate of clinical trials
- Fewer numbers subjects in trials

REGULATORY PATHWAY

- EOP2a Meetings

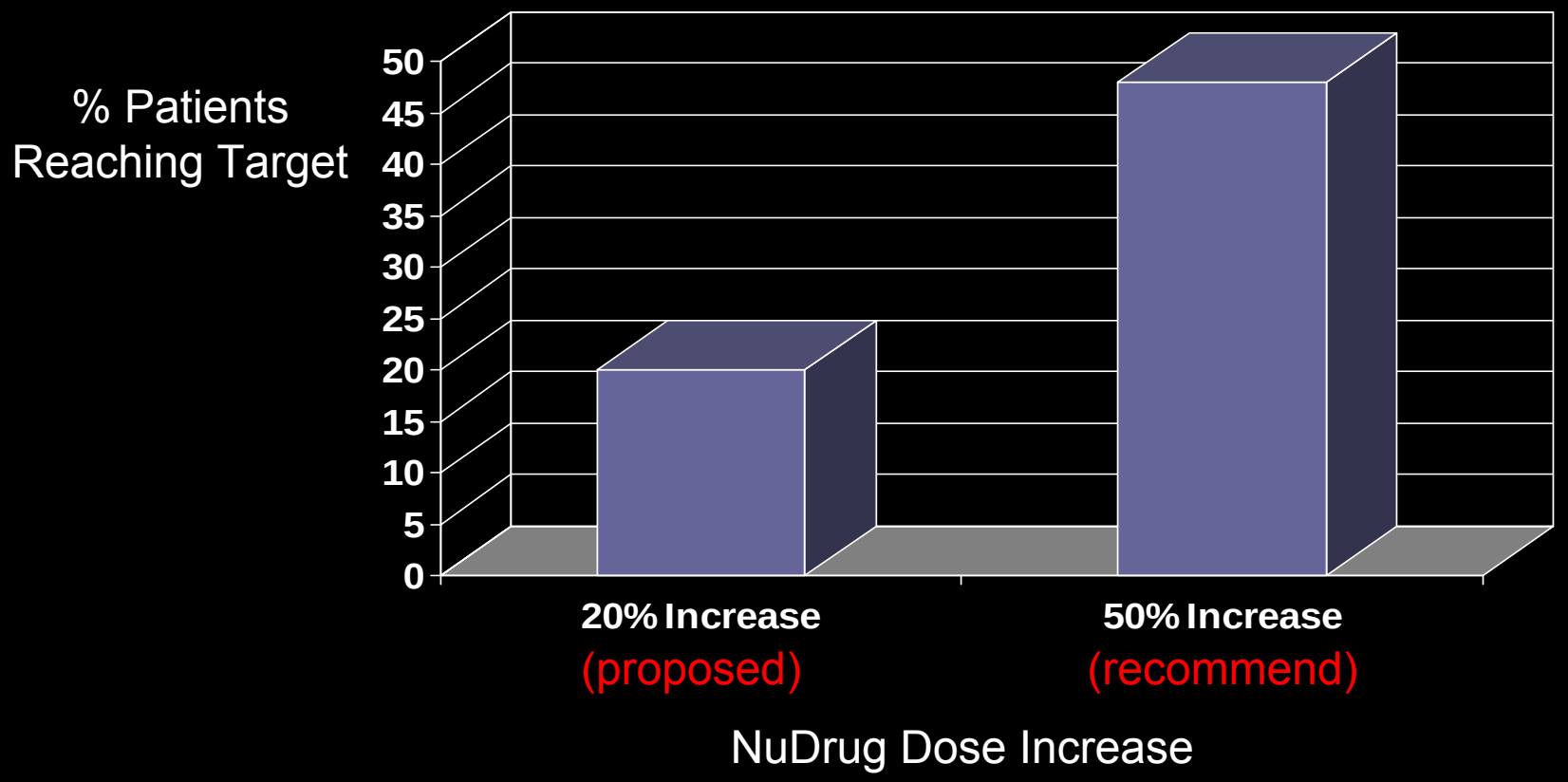
NuDrug for Rare Disease

- NuDrug is new formulation of reference product
- Clinical Development
  - Pilot dose-ranging PKPD trial in 9 patients
  - Single phase-3 trial in ~30 patients using crossover design with adaptive dosing and sample size; primary endpoint is biochemical biomarker
- Tool Used for Regulatory Decision
  - Clinical trial simulation used to assess dose-selection and sample size

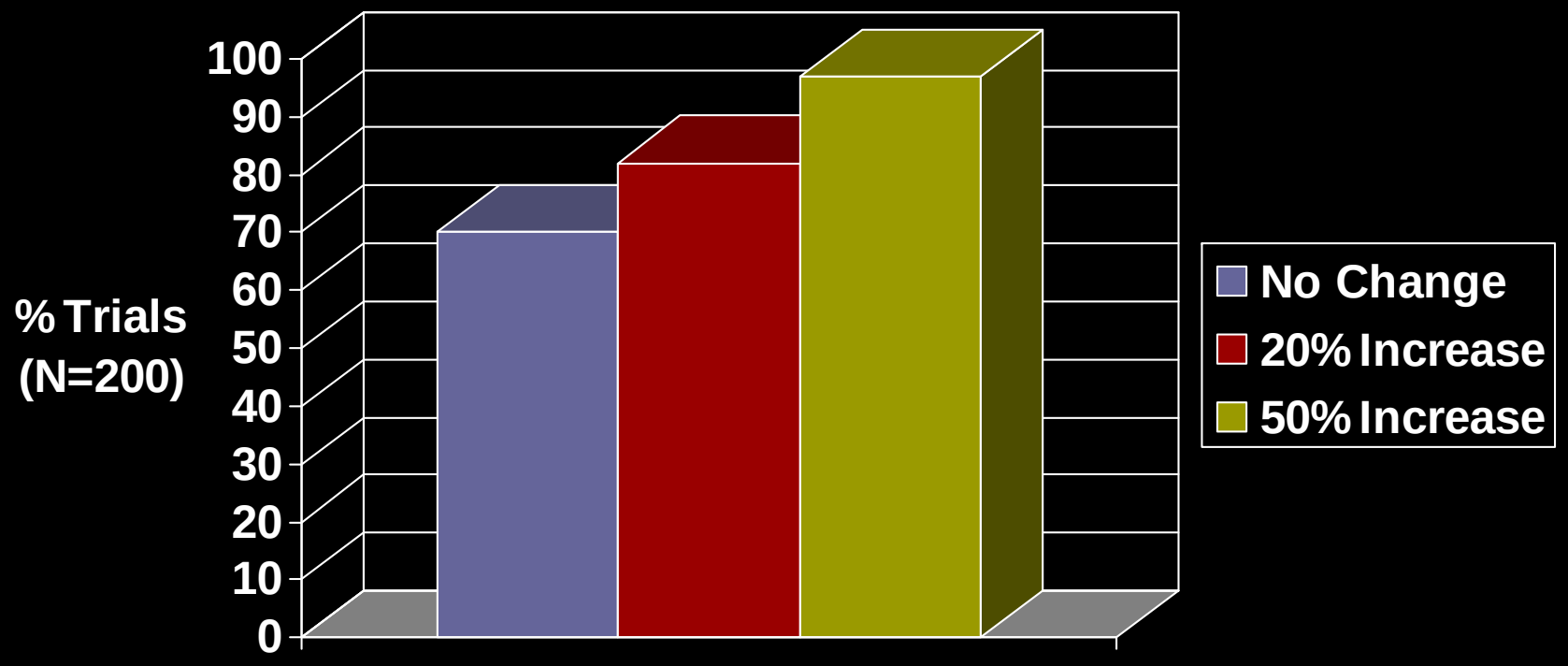
Clinical Trial Simulation to Evaluate Competing Dosing Regimens

- Evaluate proposed NuDrug dose and dose adjustment
  - 50%Total Daily Dose (TDD) of Reference + 20% dose increase for patients (proposed by sponsor)
  - 50% TDD + 50% dose increase
  - 50% TDD + No increase

Over 45% Patients Reached PD Target with 50% Dose Increase



>95% of Simulated Trials Met Endpoint with 50% Dose Increase



Knowledge Management

- Develop databases of data (*e.g.*, VXDS, clinical trials) to support future decisions
- Evaluate biomarker-outcome relationships across programs
- Provide disease-drug-trial models as a tool for drug developers

DEVELOPMENT IMPACT

- Leverage prior quantitative information to select doses and design future trials

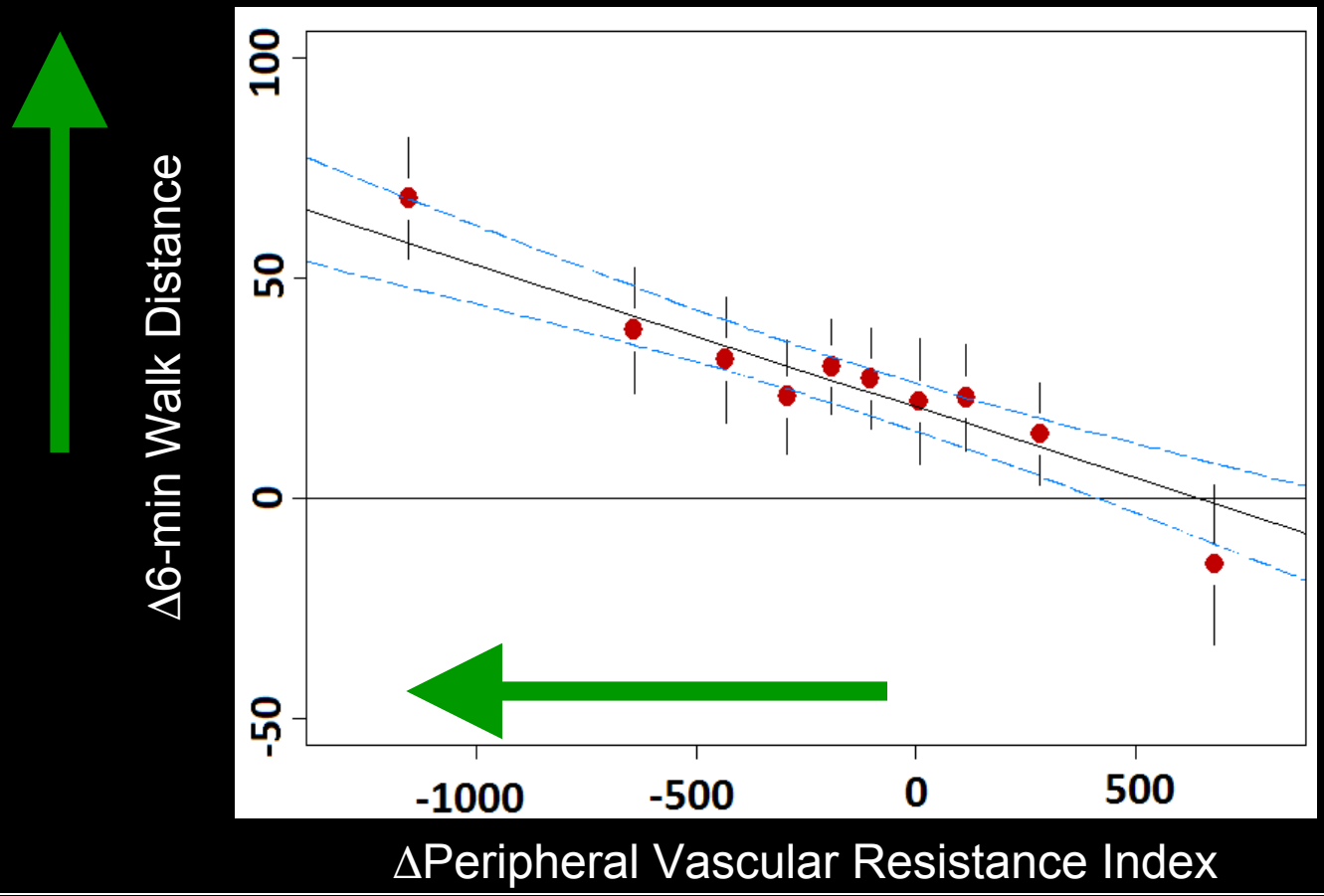
REGULATORY PATHWAY

- Critical Path modeling consortia
- Biomarker Qualification

Pediatric Pulmonary Arterial Hypertension

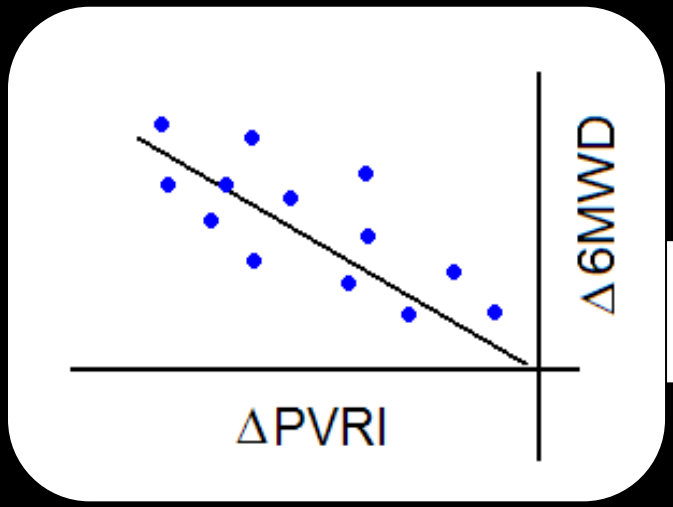
- No approved treatment for pediatrics
- No suitable measures for assessing effectiveness (6-minute walk distance) for possible approval of drugs for PAH in pediatric population
- The WHO Group I (idiopathic/familial PAH etiology) is considered to represent similar populations in children and adults

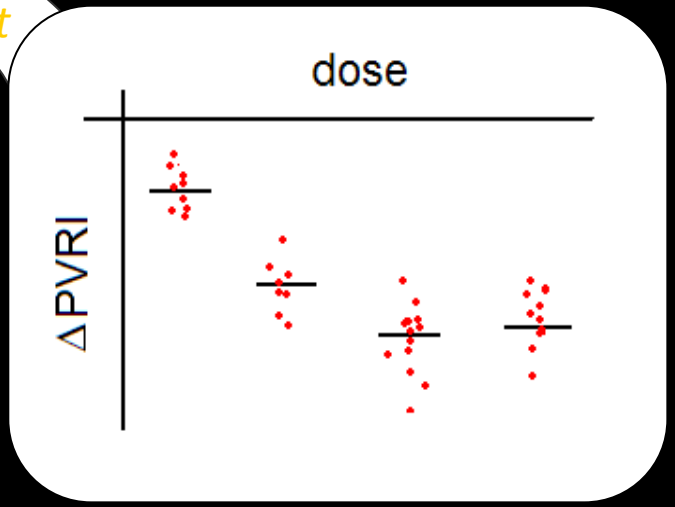
ΔPVRI is Significant Predictor of Δ6MWD in 13 Adult Trials



ΔPVRI-Δ6MWD Relationship Can Guide Pediatric Drug Development

Derive dosing based on the desired benefit in exercise capacity





Adults: Establish relationship between ΔPVRI and Δ6MWD to specify target for pediatrics.

Pediatrics: Placebo controlled, dose ranging studies performed to achieve different degrees of hemodynamic benefit.

FDA CRDAC Meeting

- "…for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in pediatric PAH population?"
  - Yes 7, No 6 and Abstain 0
- Suggestions for next steps
  - Evaluate other endpoints, *e.g.*, oxygen consumption, time to clinical worsening, right artrial pressure
  - Further validation, *e.g.*, using available data to predict study result

Good Drug Development Practices for Rare Diseases

- Understand mechanism of action, when possible
- Include biomarker of drug response for B/R
- Use innovative trial designs supported by clinical trial simulation
  - Develop disease-drug-trial models using prior data to guide future trial designs
- Use powerful methods of analyses for small clinical trials

Acknowledgements

- SEGA Case
  - Nitin Mehrotra
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  - Pravin Jadhav
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  - Larry Lesko
  - Shiew Mei Huang
  - Joga Gobburu
  - Issam Zineh
  - Dennis Bashaw
  - Gilbert Burckart
  - Rosane Charlab Orbach
  - Angela Men
  - Lei Zhang
  - Christine Le

Perspectives on Academic-Industry-Government Collaboration on Orphan Drug Development

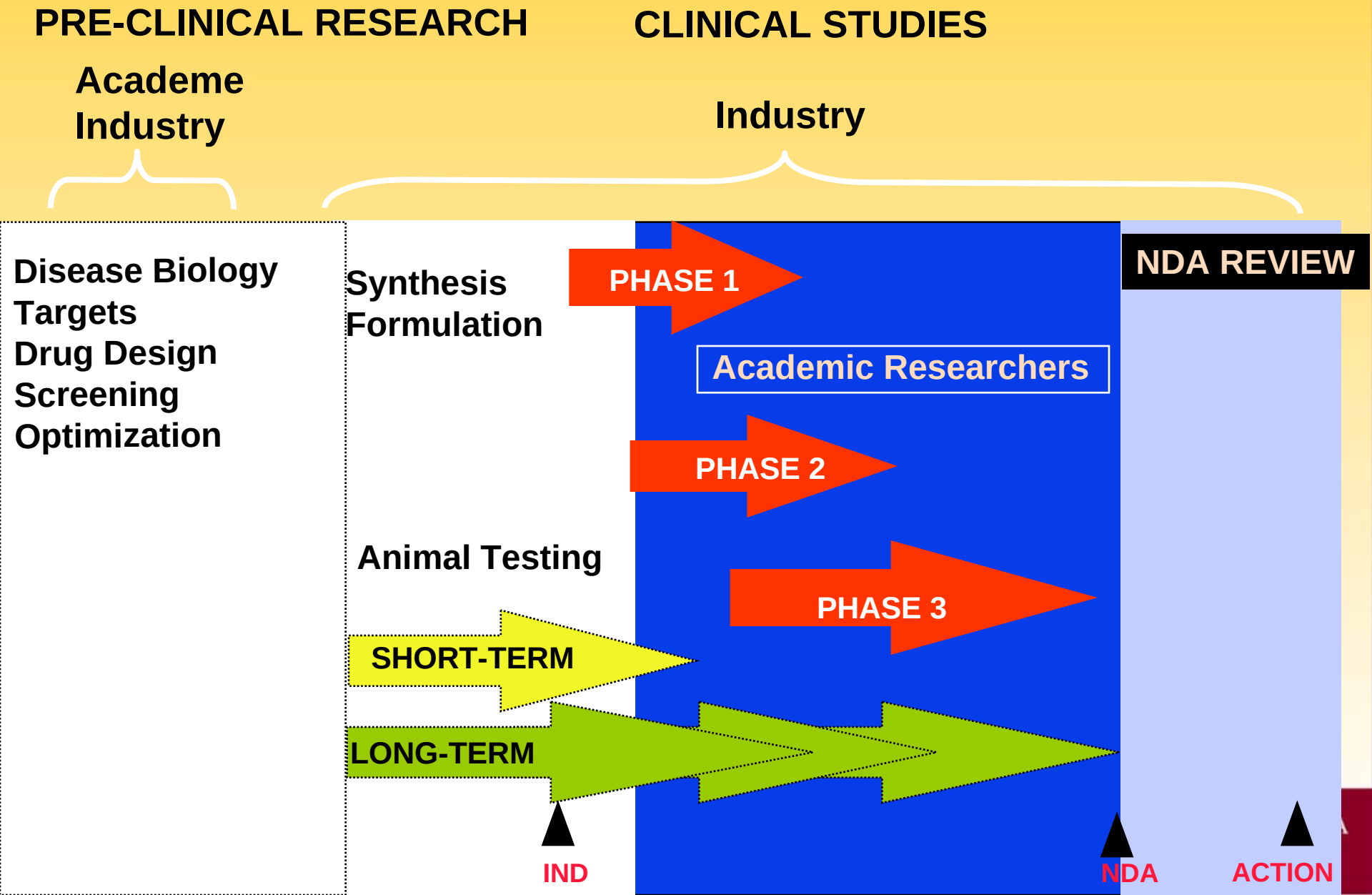
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
Center for Drug Evaluation and Research
Food and Drug Administration
March 2, 2011; Dallas, TX

James Cloyd, PharmD
Lawrence C. Weaver Endowed Chair-Orphan Drug Development

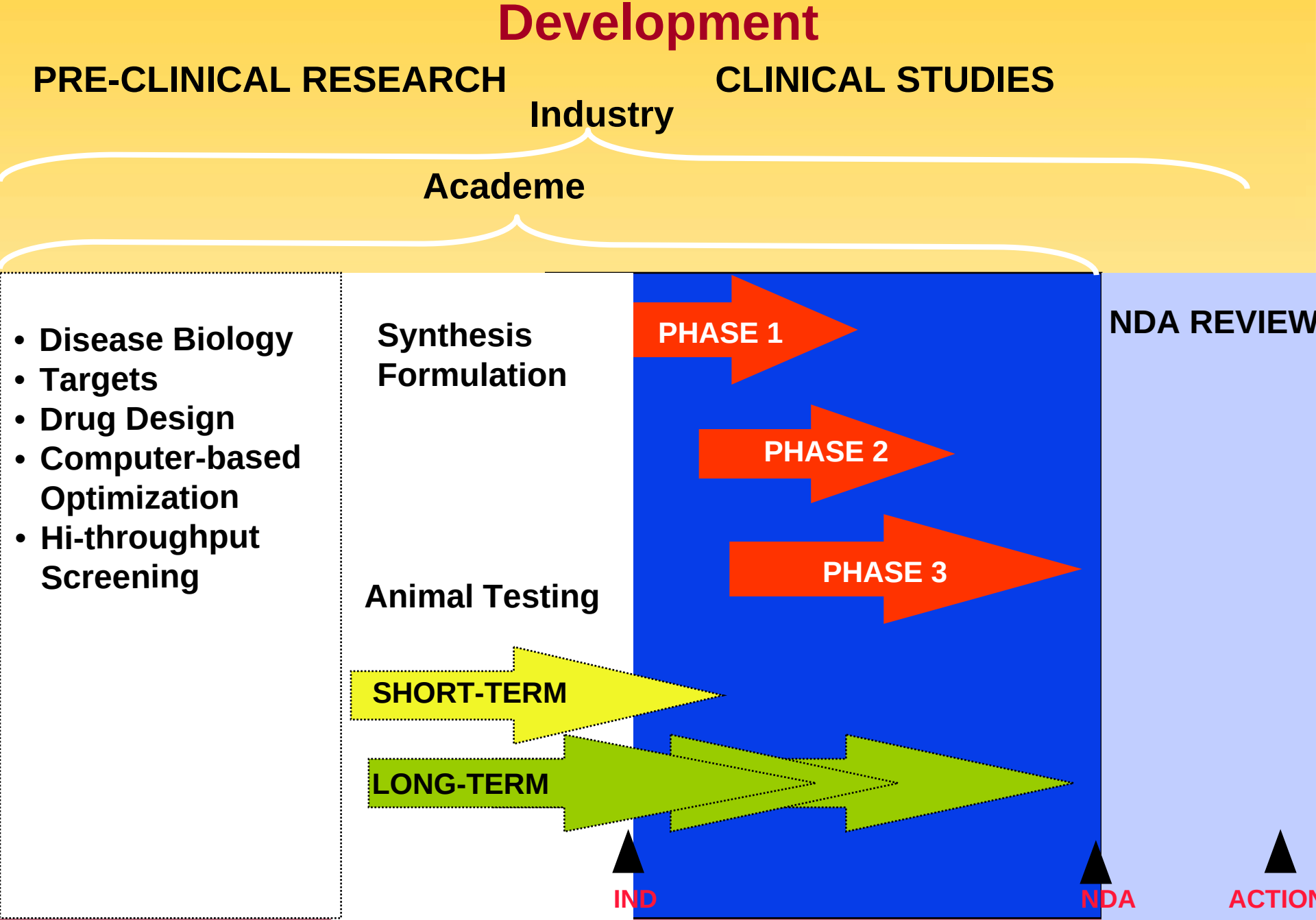
Thesis

Academic institutions can play a significant role in orphan drug development, but are presently limited by resources, regulatory issues, and funding

Conventional Paradigm for Drug Discovery & Development



New Paradigm for Orphan Drug Discovery & Development



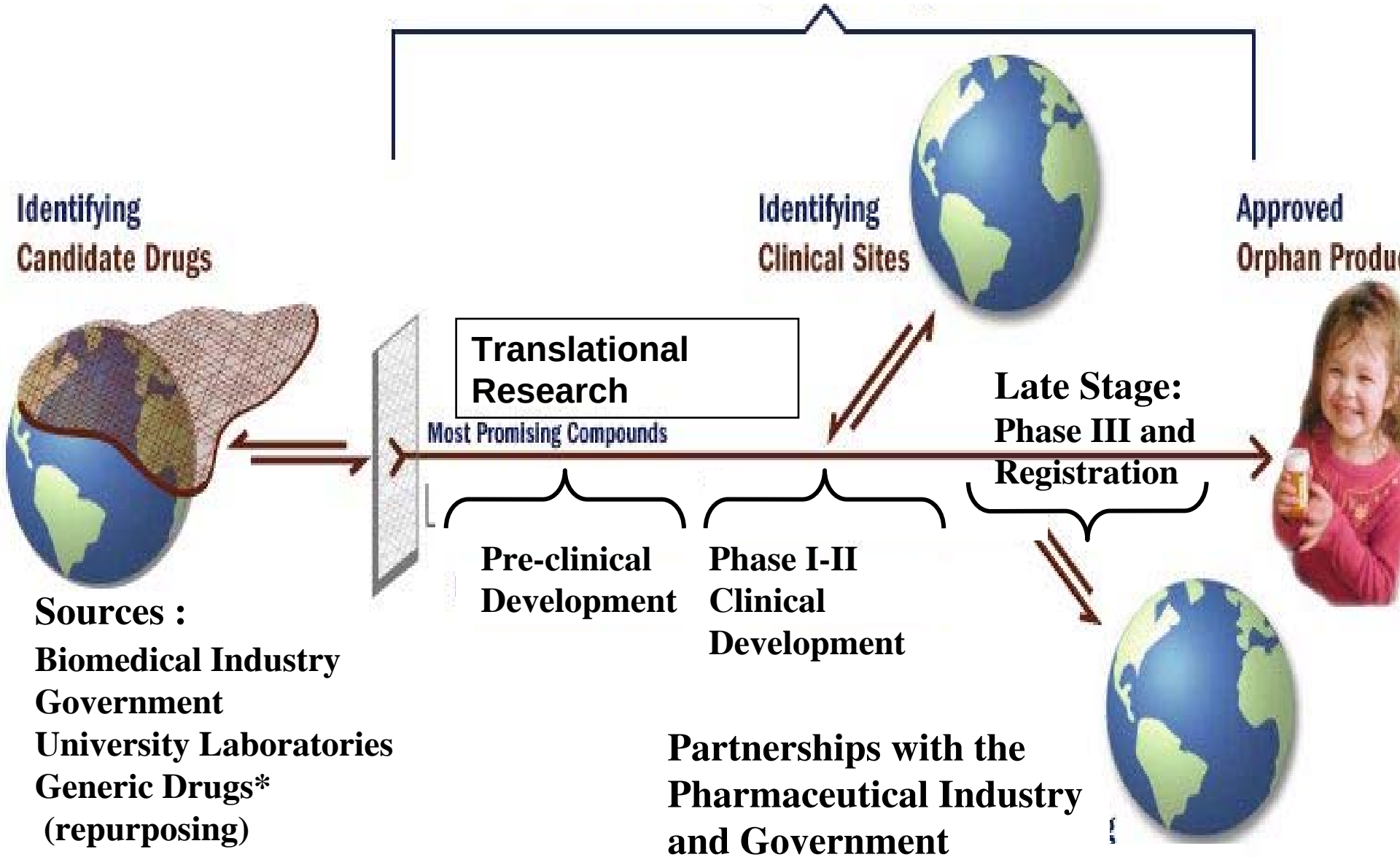
Case Studies Exemplifying Opportunities and Challenges of Orphan Drug Development at Academic Institutions

Center for Orphan Drug Research (CODR)
University of Minnesota

Mission

Improve the care of individuals suffering from rare pediatric neurological disorders through <u>research</u> on new therapies, <u>education</u> of health professionals and health profession students, and rare diseases/orphan drugs <u>advocacy.</u>

CODR Model for Research



CODR Research

Capabilities

- Pharmacometrics, Selected Animal Studies, Clinical Pharmacology and Phase I-IV Trials
- Bioanalytical Laboratory
- Drug Design, Synthesis, and Formulation
- Orphan Drug Regulatory Support
- Plus Resources of Medicine, Pharmacy, Vet Med, Public Health, and Biomedical Engineering

Case Studies in Academic-Industry-Government Collaboration on Orphan Drug Development

- **Intravenous Topiramate for Neonatal Seizures**
  - **Commercial partner-CyDex Pharmaceuticals**
- **N-acetylcysteine as Adjunctive Therapy for Adrenoleukodystrophy**

Use of Topiramate for Neonates Seizures

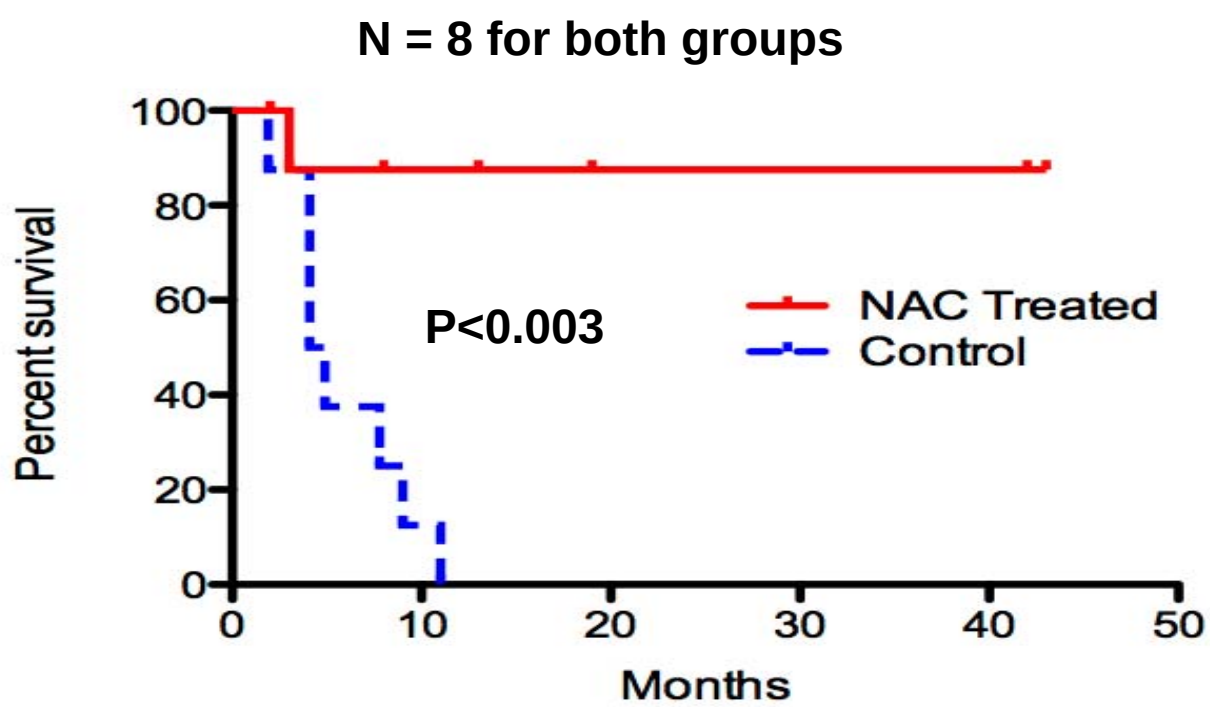
- Seizures that occur in first 28 days of life
- Annual incidence: 4,000-7,200 live births
- Therapy: phenobarbital, phenytoin
  - Open-labeled trials without placebo: 40-45% response rate
  - Tx results in significant acute and long-term AEs
- Topiramate
  - Approved as antiseizure drug for patients ≥ 2 yrs
- Development Plan: 2008-?
  - Adult patients and volunteers (N = 32) completed
  - Amended IND to study younger patients: 2011
  - Studies in older children and pilot PK study in newborns: 2113
  - Completion of Phase III trial by 2017+!)
  - Data and expertise shared with CyDex

Issues in Developing IV Topiramate

- Funding tends to be short term (1-3 yrs) with long lead times
  - FDA Orphan Grants, Epilepsy Research Foundation, NIH TRND
- Maintenance of research team (project time table = 10 yrs
- Early and timely guidance from FDA
- Design of clinical trials-IRB approval of placebo-controlled designs
- Reliance on commercial sponsor to market product

Use of N-acetylcysteine for Late-stage Adrenoleukodystrophy (ALD): A True Orphan

- Rare genetic disorder affecting boys: prevalence 1:20,000 births
- If disease progresses to late stage, death in 3-5 yrs
- In early 2000s, UMN begins hematopoietic stem cell transplantation
- Initial results disappointing



Orchard et al, University of Minnesota, 2009

Issues in Developing NAC for ALD

1. IV formulation: Acetadote®, an orphan product (exclusivity expires 2011)
2. Who funds the clinical trials, especially long-term outcome studies?
3. Is there a mechanism to change the product label when there is no commercial sponsor?
4. Does #3 matter, if research is published in peer-reviewed journals?
5. Is there a pathway to commercialization and product support? If not, so what?

Challenges in Getting Academic Groups Involved in Orphan Drug Development

Academic Researchers and Centers

7. Often not interested in commercialization

6. Do not operate GMP and GLP facilities including animal toxicology

5. Unable to secure NIH funding for drug development

- **Particularly for re-purposing of available drugs**

4. Unaware of federal programs that support orphan drug development

3. Unable to sustain development programs during funding gaps

2. Difficulty in finding industry partners interested in commercializing orphan drug

And the top reason why academicians reluctant to participate in drug development

1. Fear and loathing of regulatory requirements related to drug development and unfamiliarity with FDA procedures

Academic-Industry-Government Collaborations: Opportunities

Academic Centers

- **Possess most, but not all, the personnel and facilities for drug discovery and development**
- **Are increasingly involved in designing and performing Phase I-IV studies**
- **Are expanding capabilities in drug discovery and pre-clinical development**
- **Are accustomed to competing for federal research funding**
- **Commonly serve as centers for care of those with rare disorders**
- **Frequently participate in clinical research consortia**

Harnessing the Potential for Academic Centers in Discovery and Development of Orphan Drugs

- Expand efforts to make academicians aware of opportunities and funding for orphan drug development
- Create mechanisms to ensure program continuity
- Enhance and expand government efforts to assist academicians in developing drugs for rare and neglected disorders

  e.g. assistance with INDs, GMP and GLP issues, guidance in adhering to regulations, collaboration as well as oversite
- Integrate drug discovery and development into rare disease research
  - e.g. NIH-funded Rare Disease Clinical Research Network

Perspective

- Academic centers can and should play a greater (complementary) role in the development of orphan drugs

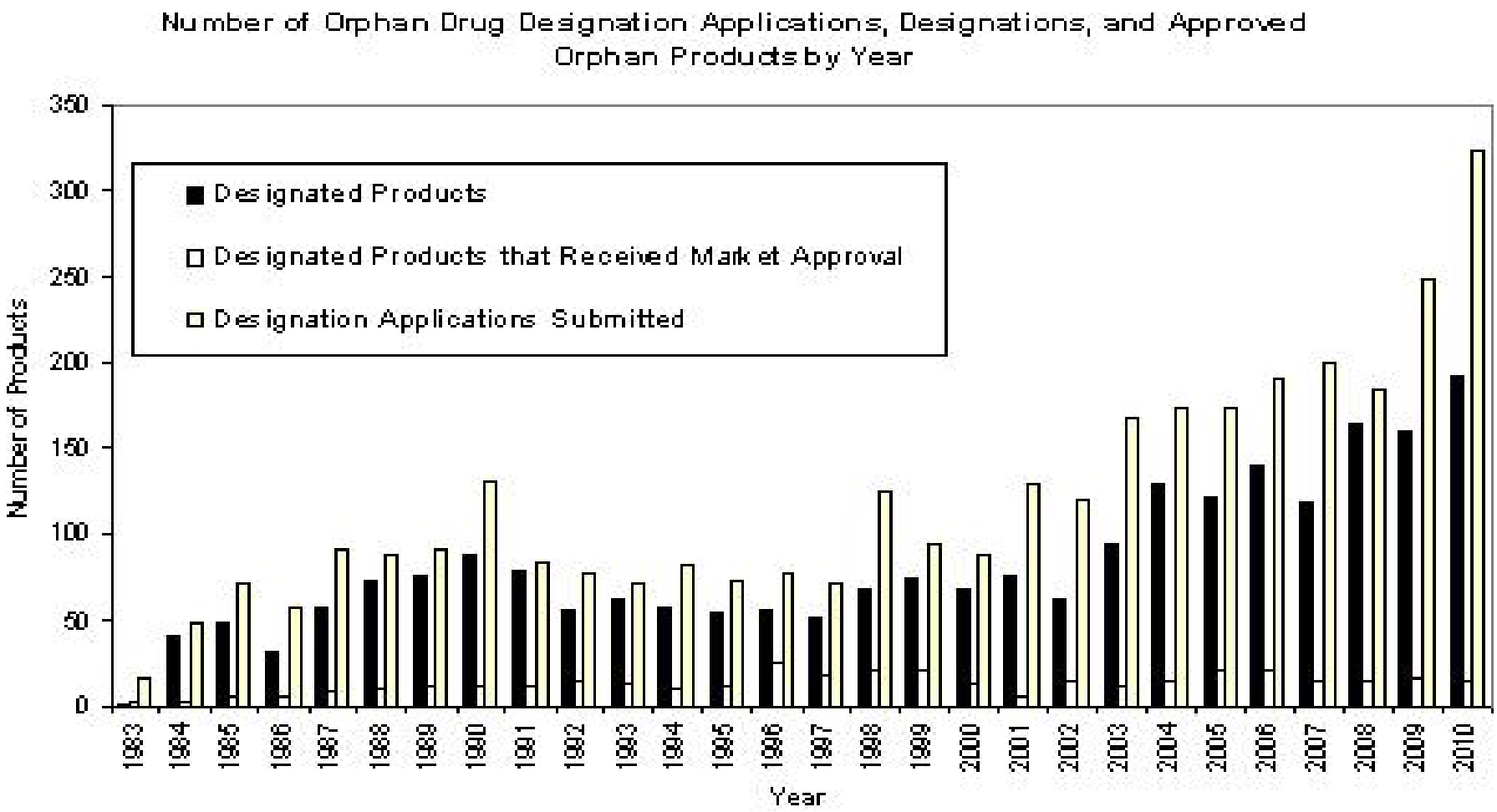
- Early signs of growing involvement are encouraging
  - Greater awareness of rare and neglected disorders by society, government, and the pharmaceutical industry
  - Targeted funding by NIH, FDA, venture philantrophists, and patient advoacy organizations for pre-clinical and clinical development
    (NIH TRND, FDA Orphan Grants, Michael J. Fox Fdn)
  - Increasing involvement of academic groups

"Prediction is very difficult, especially of the future."
(Niels Bohr)

FDA Designation of Orphan Products

Year	No. Approved	No. Designated	No. Designation Apps
1983	2	1	16
1984	3	41	48
1985	6	48	71
1986	6	32	58
1987	9	58	91
1988	10	73	88
1989	12	76	91
1990	12	88	131
1991	12	79	84
1992	14	56	77
1993	13	62	72
1994	11	58	82
1995	12	55	73
1996	25	57	77
1997	18	51	72
1998	20	68	125
1999	20	74	94
2000	13	69	88
2001	6	76	129
2002	14	62	121
2003	12	95	168
2004	14	130	174
2005	20	122	175
2006	22	141	190
2007	15	119	200
2008	15	165	185
2009	17	160	250
2010	14	192	323
TOTAL	**367**	**2308**	**3353**

Karst K. FDA Law Blog, Jan



Karst K, FDA Law Blog, Jan 31, 2011

FDA Next Steps

Anne Pariser, M.D.
Office of New Drugs, Rare Diseases Program
Center for Drug Evaluation and Research
Food and Drug Administration

Rare Diseases

- Rare diseases
  - One of the most rapidly expanding areas of research and clinical development
  - Remarkable progress in molecular biology, pharma/biotech science and novel target identification in recent years
    - ~7000 rare diseases – ~85% genetic
      - Increasing by ~100 new diseases/year
      - Common diseases being divided into medically plausible subsets
        - » E.g., alk+ subset of NSCLC

RD Clinical Development Challenges

- Rare disorder with few patients available for study
  - Chronic, progressive, serious, life-limiting and life-threatening with unmet medical need
  - Natural history incompletely understood
    - Rate of progression variable
  - Specific endpoints, outcome measures, tools, instruments and biomarkers usually lacking
    - From regulatory standpoint, no precedent no “validated” or qualified endpoints, biomarkers or surrogates
  - Datasets (efficacy and safety) will almost always be small
    - Often limited by what is feasible
  - Often, pediatric population
  - Target tissue delivery (e.g., CNS)

Orphan Drug Act History

- ODA
  - Highly successful
    - >360 approvals, >2200 designations
    - 90% of Orphans in CDER
      - Remaining 10% in CBER
        - » Mainly blood-derived products (e.g., coagulation factors)
  - In past few years
    - ~1/3 of all NME approvals are Orphan products
    - 2/3 of therapeutic biological product approvals

CDER Orphan History 2006-2010

- CDER's marketing applications for NMEs and new biologics 2006-2010*
- Orphans are 30% of all new applications
  - 13 biologics, 22 drugs approved
  - 29 different indications
    - 10 different therapeutic areas, ~1/3 oncology
  - 28 different companies (~1/3 each S, M, L)
  - Disease prevalence ranges ~50-180,000 patients (median 43k, mean 58k)

*source: CDER/Office of New Drugs Rare Diseases Program database project, Pariser et al

CDER Orphan History (2)*

- 75% of Orphan marketing applications are approved (vs. 70% for non-rare)
- 20% of rare disease approvals are for first-in-disease indications
  - Compared to 3% for non-rare
  - 75% of first-in-disease therapies from small companies

*source: CDER/OND RDP database project, Pariser et al

Regulatory Pathways to Approval

- Two possible pathways to approval for serious/life-threatening disorders
  - Regular approval
    - Aka standard approval, full approval
  - Accelerated approval
    - Based on a surrogate endpoint "reasonably likely to predict clinical benefit"
    - For new drug products to treat serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments

Evidentiary Standard for Approval

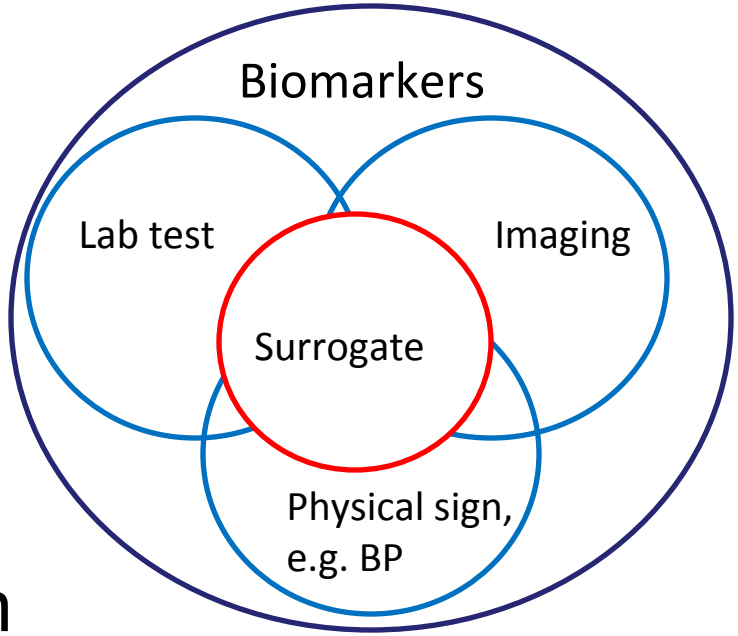
- To be approved, all drugs (Orphan and non-Orphan) must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
      - Improvement or delay in progression
  - Evidence of effectiveness [PHS act 505(d)]
    - "Evidence consisting of adequate and well–controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports"

Accelerated Approval

- Accelerated approval (§314.510, Subpart H)
  - "FDA may grant marketing approval for a new drug product on the basis of ***adequate and well-controlled clinical trials*** establishing that the drug product has an ***effect on a surrogate endpoint that is reasonably likely to predict clinical benefit***"
  - Requires postmarketing verification study to verify and describe its clinical benefit.
    - Postmarketing study must also be adequate and well-controlled
    - Should be conducted "with due diligence".

Surrogate vs. Biomarker

- Biomarker ≠ Surrogate
- Biomarkers have many potential roles
  - Exploratory/preliminary/ PD activity
  - Patient or dose selection
  - Safety markers, etc.



Flexibility

- Regulations leave room for flexibility:
  - “FDA is required to exercise its scientific judgment to determine the kind and quatity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.” (§314.105)

CDER History 2006-2010 (3)

- Level of evidence – most programs unique and non-traditional
  - E.g., Single trial + other evidence supporting application
    - E.g., historical control, evidence in a related population, non-traditional study designs, PD endpoints

"Non-Traditional"

Elsevier
BusinessIntelligence
Essential Insight for the Healthcare Industry
Formerly F-D-C Reports & Windhover Information

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

"The Pink Sheet" DAILY
Friday, February 18, 2011

CSL Behring's Corifact Clears FDA On 14-Patient Trial

FDA is reaffirming its willingness to clear drugs for orphan conditions on very unusual data sets with its approval of **CSL Behring**'s *Corifact* for prevention of bleeding in people with congenital Factor XIII deficiency.

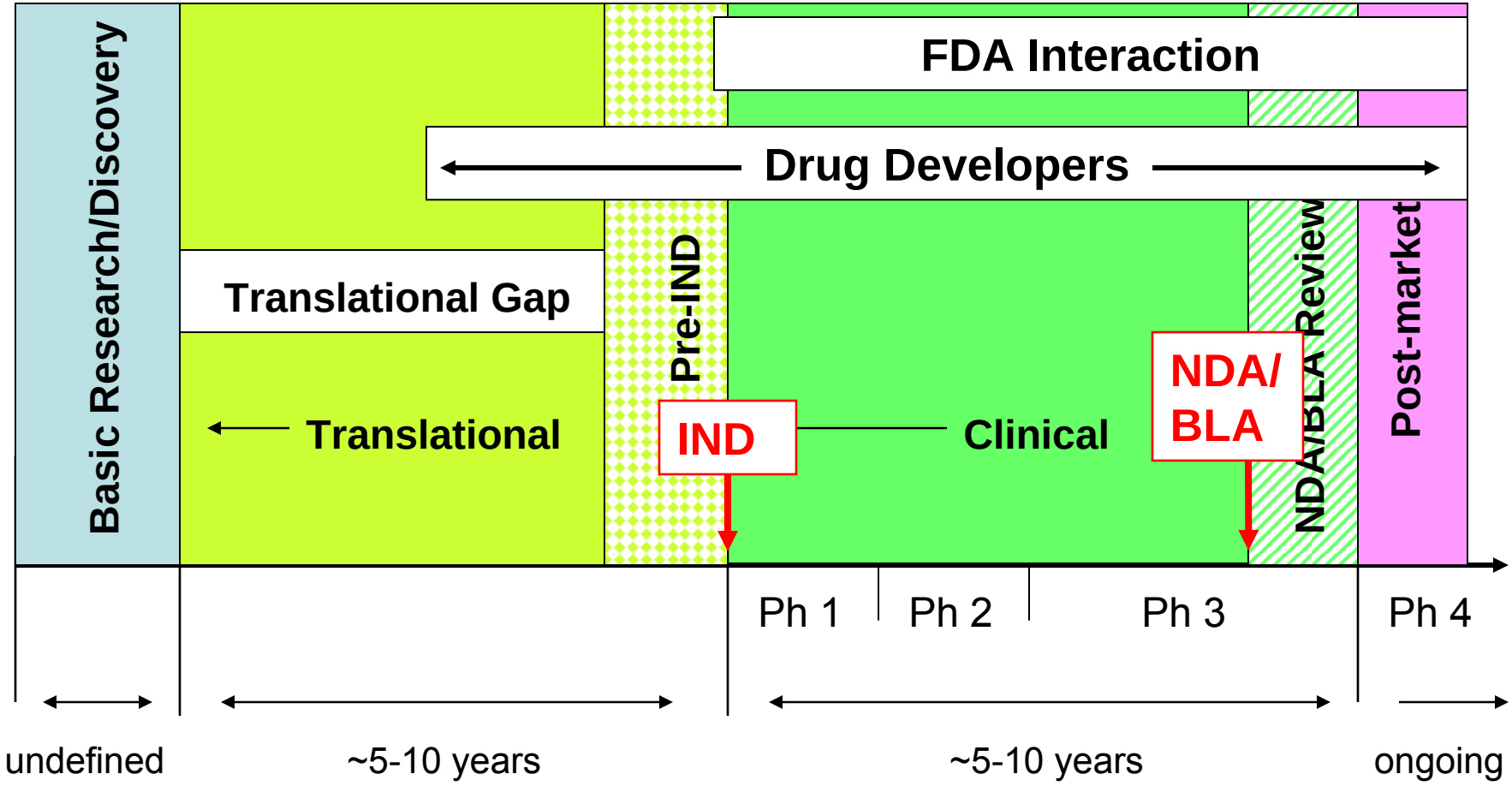
Elsevier, Inc. The Pink Sheet, February 18, 2011 www.thepinksheetdaily.com.

What are our Plans for the Future?

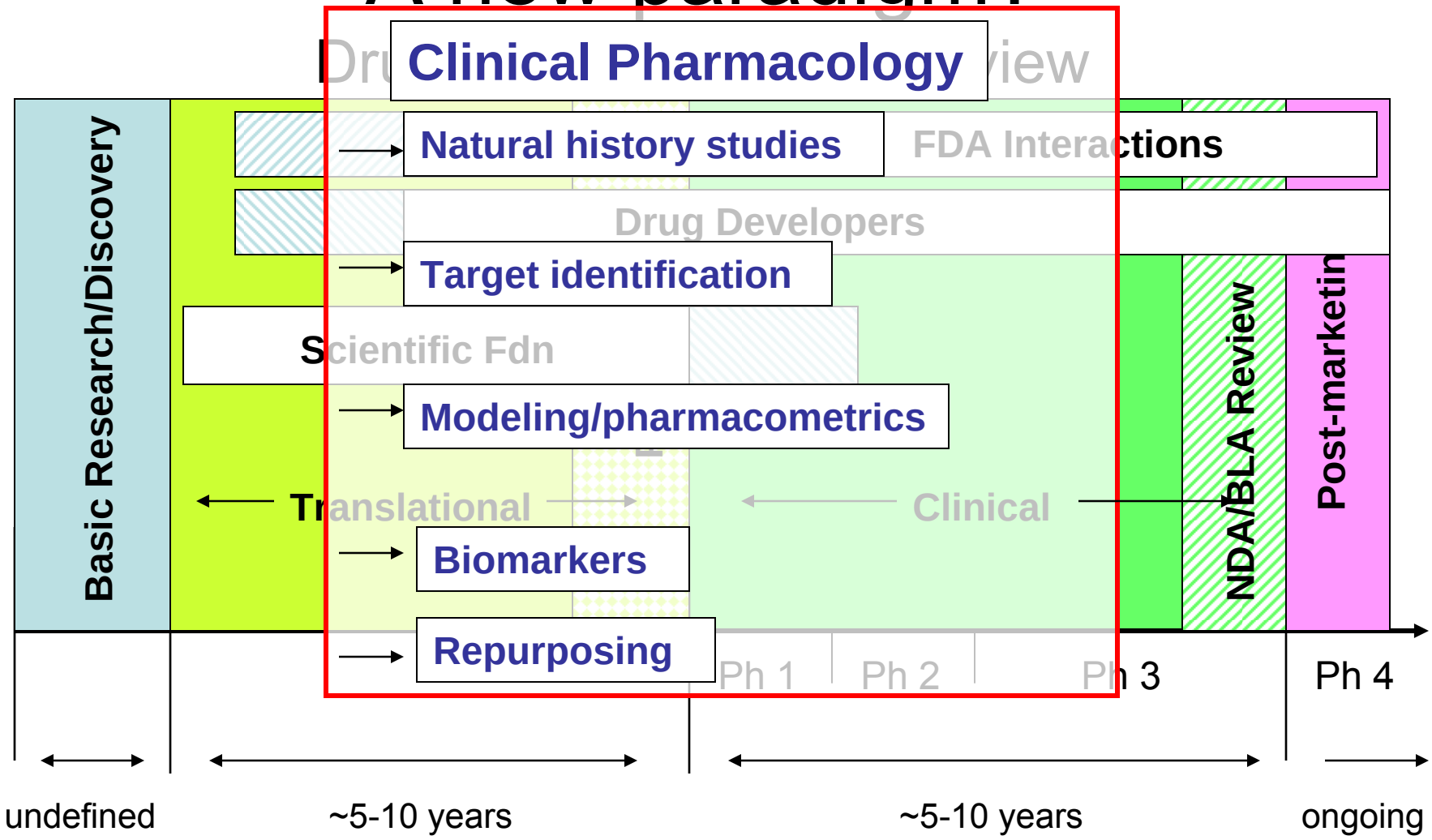
- Addressing the scientific challenges
  - Institute of Medicine (IOM) October 2010 "Rare Diseases and Orphan Products: Accelerating Research and Development"
    - Central message: Implementation of an integrated national strategy to promote rare disease research and product development
      - Collaboration
      - Timely application of advances in science
      - Appropriate use and development of trial design and analytic methods
      - Creative strategies for sharing resources

Traditional Drug Development

Overview



A new paradigm?



Opportunities for Collaboration

- Milestone meetings:
  - Pre-IND, EOP1, EOP2A, EOP2, pre-NDA/BLA
    - EOP2A meeting – to facilitate interaction btw FDA and sponsors for
      - "clinical trial design employing clinical trial simulation and quantitative modeling or prior knowledge…
      - designing trials for better dose response estimation and dose selection…
      - related issues"
    - EOP2A especially critical for rare disease applications

Goal

- Comprehensive clinical development based on a strong scientific foundation

From here….

To there

Areas of Focus

- Clinical Pharmacology critical piece in rare disease product development
  - Understand the disease
  - Early candidate and target identification
  - Decision tree
    - Best practices by situation
  - Building drug's entire "story"
    - PK/PD, dose identification, biomarkers at all phases of development
    - Support evidentiary standards for approval

Next Steps

- Map out clinical development programs as early as possible
  - Essential first step is scientific foundation support (e.g., natural history study)
    - Can be started even before a candidate drug is identified
  - Early and frequent communication with FDA is essential
- Make the most of early phase development
- All the evidence will be considered in rare disease applications
- Collect/develop/explore best practices to move more products into development
  - Quantitative model-based (pharmacometric) approach
  - Other tools, study designs, endpoints

FDA's New Initiatives

- Rare Disease Review Group
  - Legislative mandate
    - Open public hearing June 2010
    - Report due March 2011, Guidance Sept 2011
- Comprehensive database analysis in progress
  - Successes, barriers, advice generation expected
  - Inform paradigms for rare disease drug development
- New Rare Diseases Program in CDER
  - Established Feb 2010
    - Support and accelerate rare disease drug development
- Numerous collaborations
  - NIH, NIH TRND, NORD
  - Workshops, scientific development
  - Repurposing database – OOPD, OCP, NIH TRND
  - Internal and External rare disease-specific training courses
    - Next investigator training course October 2011

RARE DISEASE DAY USA

Alone we are Rare. Together we are Strong.

02.28.2011

Contact information

- CDER Office of New Drugs Rare Diseases Programs
  - Anne Pariser, M.D. anne.pariser@fda.hhs.gov
  - Larry Bauer, R.N., larry.bauer@fda.hhs.gov
  - Website

  http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm221248.htm

References

1. Formal meetings between the FDA and sponsors or applicants
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf
2. End-of-Phase 2A Meetings
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079690.pdf
3. Providing clinical evidence of effectiveness for human drug and biological products
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf