Rare Diseases, Orphan Drugs and Innovation: US FDA Perspective

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Innovation

- Innovation (in-*uh*-**vey**-sh*uh*n)
  - Something new or different introduced
  - Introduction of new things or methods
  - The act of introducing something for the first time
  - Making changes in anything established

Outline

- Rare diseases and orphan drug innovation history
- The coming wave of Orphan products
- How will regulatory agencies meet the challenge: FDA perspective
- Key points

Early Orphan History

- Rare diseases have often led the way for medical advances
- Early example – LDL cholesterol and atherosclerosis
  - 1938 Carl Müller described familial hypercholesterolemia (FH)
  - ~1963 Avedis Khachadurian described 2 FH forms
    - homozygous (HoFH) and heterozygous (HeFH)
  - 1985 Joseph Goldstein and Michael Brown shared Nobel Prize in Medicine for research on genetic regulation of cholesterol metabolism
    - Identified HMG-CoA reductase and inability to remove LDL from the blood in HoFH children and their HeFH parents[1]

[1]Goldstein JL, Brown MS, Proc Natl Acad Sci USA 1973;70(10):2804-2808.

Early Orphan History (2)

- 1987 lovastatin first HMG-CoA reductase inhibitor approved in US
- ~60 million Americans receiving lipid-lowering therapy
- All-time highest grossing prescription drugs in US
  1. Atorvastatin (Lipitor) $7.2 billion
  2. Esomeprazole (Nexium) $6.3 billion
  3. Clopidogrel Plavix $6.1 billion
  8. Rosuvastatin (Crestor) $3.8 billion
  10. Erythropoietin alfa (Epogen) $3.3 billion

Early Orphans (3) -- FH

- HoFH – 1 in a million
  - Still no drugs approved in US for its treatment
  - LDL apheresis, liver transplantation
- HeFH – ~1:500 in many populations
  - Numerous therapeutics, e.g., statins, bile acids, other drugs
- Investigational agents in clinical trials in HoFH
  - Clinicaltrials.gov lists 22 studies in various phases, e.g., Phase 3
  - Anti-sense oligonucleotide (AON) (mipomersen)[2]
    - Targets mRNA for apolipoprotein B
  - Microsomal triglyceride transfer protein (MTP) inhibitor (lomitapide)[3]
    - MTP necessary for VLDL assembly and secretion

[2]Visser ME et al. Mipomersen…R DB PC trial. Eur Heart J 2012;33(9):1142-1149

[3]Cuchel M et al. Inhibition of MTP in FH. N ENgl J Med 2007;356(2):148-156.

Orphans –-Mid-term History

- Hematopoietic Neoplastic Diseases with Orphan Drugs Approved
  - Acute Myelogenous Leukemia (AML)
  - Acute Promyelocytic Leukemia (APL)
  - Chronic Myelogenous Leukemia (CML)
  - Acute Lymphocytic Lymphoma (ALL)
  - Chronic Lymphocytic Leukemia (CLL)
    - B-Cell CLL (B-CLL)
  - Non-Hodgkins Lymphoma (NHL)
  - Hodgkins lymphoma (HL)
  - T Cell Lymphoma (TCL)
  - Peripheral T Cell Lymphoma (PTCL)
  - Cutaneous T Cell Lymphoma (CTCL)
  - Multiple Myeloma (MM)
  - Myelodysplastic Syndrome (MDS)
  - Myelofibrosis (MF)
  - Anaplastic large cell lymphoma (ALCL)

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Orphan Midterms (2)

- Orphan drugs that have changed practice standards –- partial list
  - Imatinib for CML
  - ATRA and ASO_3 for APL
  - Rituximab for CLL and NHL
  - Azacitidine, decitabine and lenalidomide for MDS
  - Bortezomib, phenylalanine mustard, thalidomide and lenalidomide for MM

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Evolution of Imatinib

CML
- P210Bcr-Abl protein kinase leads to genetic instability and unregulated signals for cell proliferation and survival

→

Imatinib
- Small molecule binds to ATP binding site of Abl kinase to inhibit phosphorylation of P210Bcr-Abl
- Induces CCyR in 85% of CP CML

↓

CML (n~2100 pts 1st and 2nd line)
- 2nd line Accelerated AP 2001, 1st line AA 2002
- 2nd line full AP 2003, 1st line full AP 2009

←

Pediatric CML
- 2nd line AA 2003, n=14
- 1st line AA 2006, n=51

↓

Ph+ ALL – related disease
- 2nd line AP 2006, n=50

→

Different diseases, different kinase mechanism
- MDS with mutated PDGF, n=7
- GIST mutated c-Kit, n=147
- Hypereosinophilic syndrome, Abl, Kit or PDGRF, n=14
- DMF protuberans, PDGF 7(17/22) n=12
- Aggressive systemic mastocytosis, Alb, Kit or PDGFR, n=5

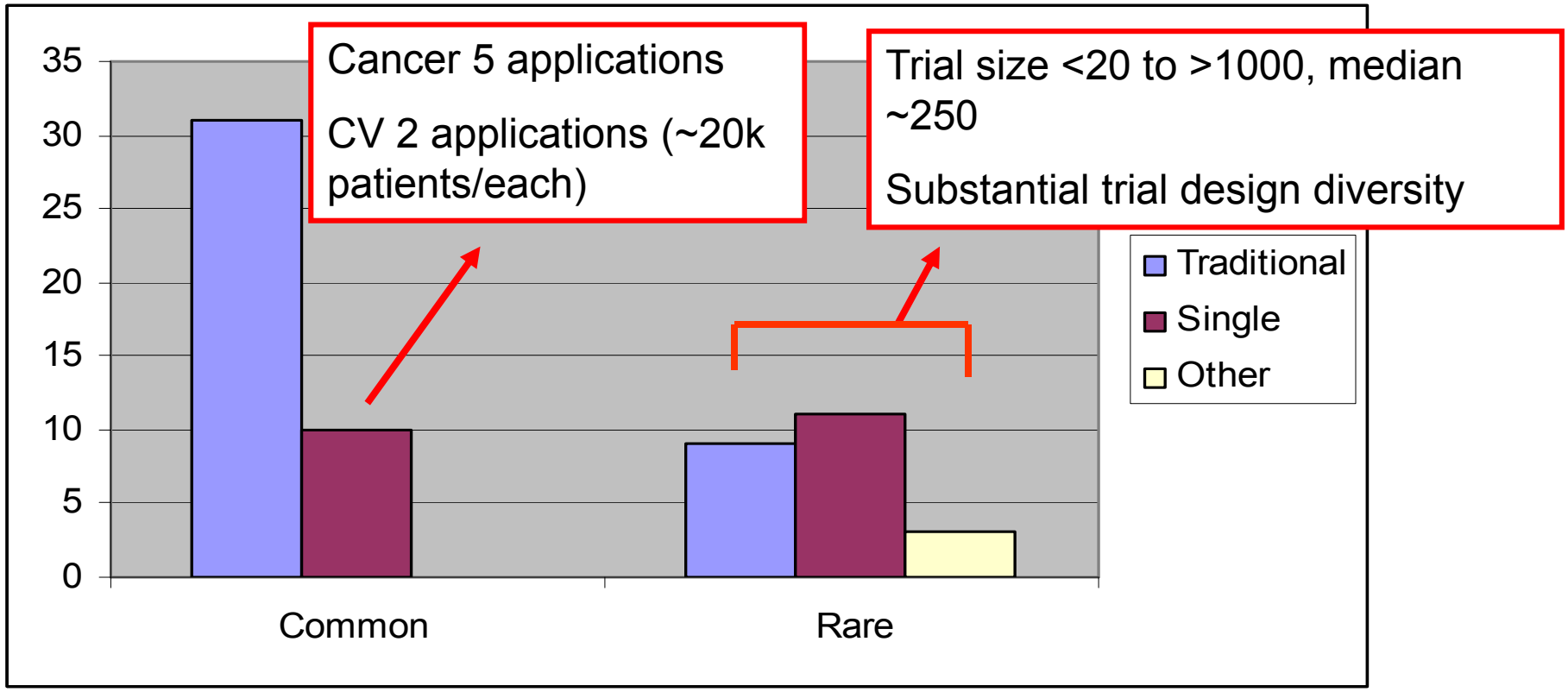
With thanks to Albert Deisseroth M.D., Ph.D., US FDA DHP

Recent Orphan History

- From January 1, 2010-May 20, 2012 at CDER
  - 46 Rare/Orphan Approvals
    - 23 NMEs and new biologics, ~1/3 of CDER's total
    - 23 repurposed
  - First-evers
    - Companion diagnostics
    - ~50% no regulatory/disease precedent
      - Vs. common disease <10%
  - Smaller patient populations
    - Common disease → targeted subpopulation
      - E.g., crizotinib for ALK+ non-small cell lung CA
      - vemurafenib for BRAF+ melanoma
    - Rare disease → targeted subpopulation
      - E.g., ivacaftor for Cystic Fibrosis

Recent History -- Level of Evidence

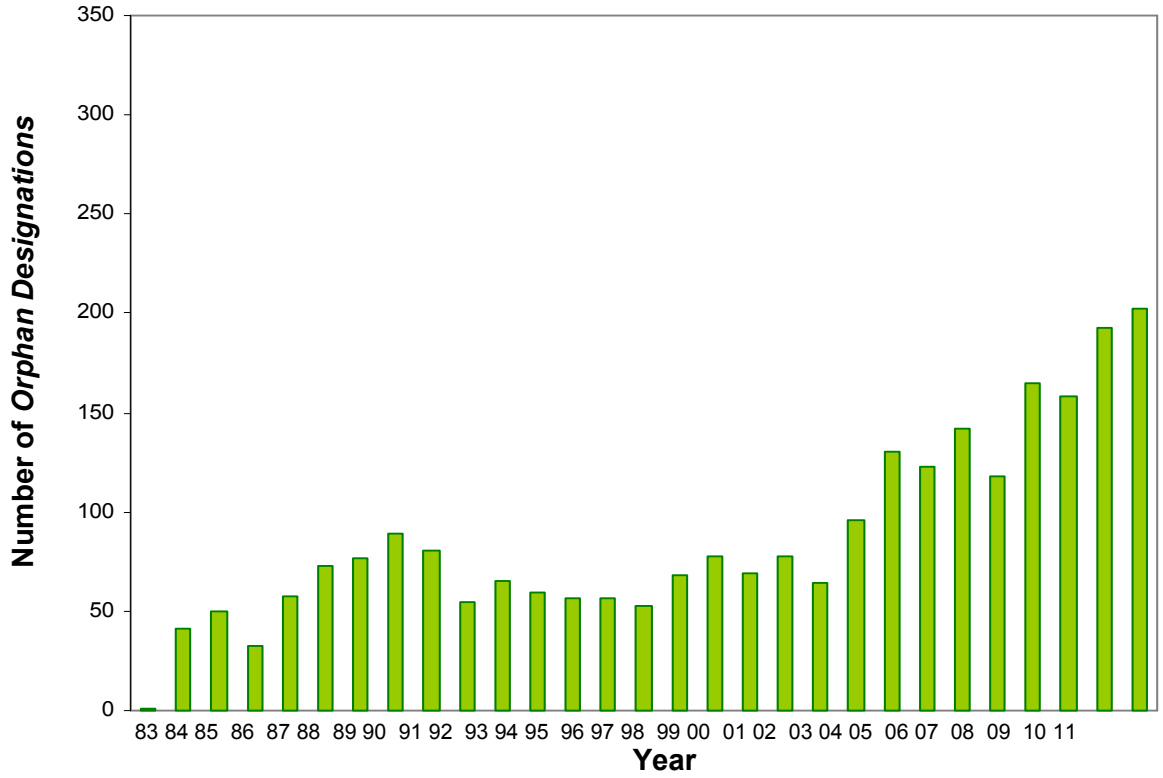
2010-2012 NMEs and New Biologics



The Coming Wave of Orphan Products

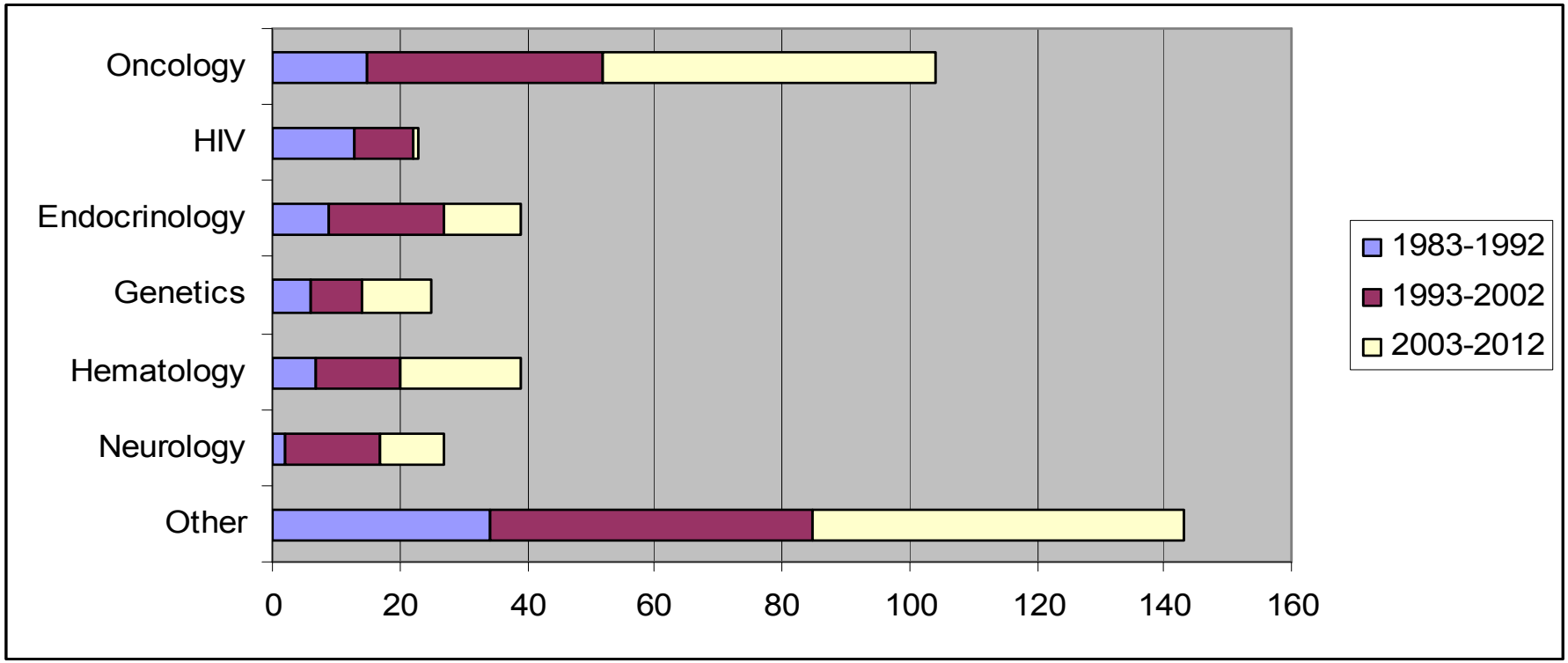
Orphan Designations

~2600 Products have received Orphan Designation
-- Products are designated in pre-IND or IND phases



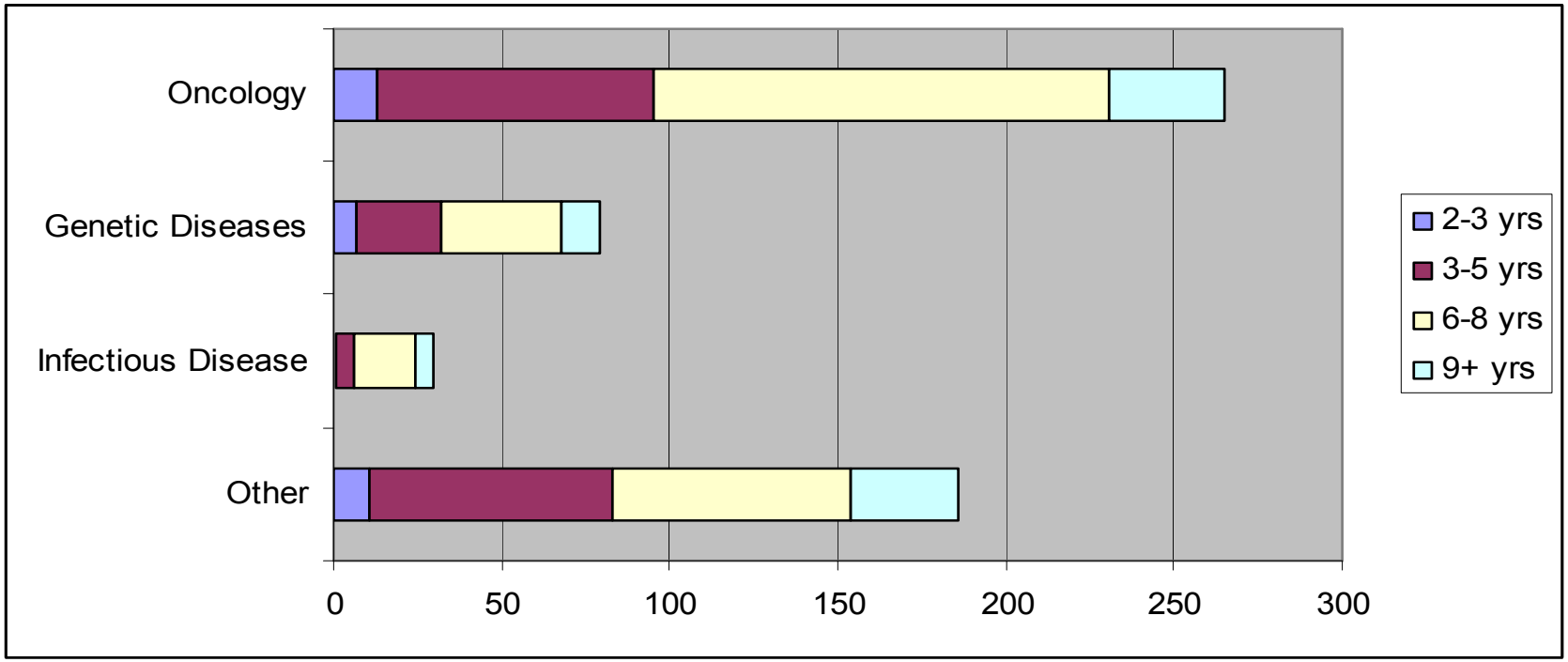
Slide courtesy of Gayatri Rao, MD, JD, Office of Orphan Products Development ,US FDA. Source: Search Orphans Drug Designations and Approvals, available at: ww.accessdata.fda.gov/scripts/opdlisting/oopd/

Orphans by Therapeutic Area 1983-2012



Source: Search Orphans Drug Designations and Approvals, available at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/ Last accessed May 20, 2012

Future Projections/Estimates--
Orphan Designated Products



Source: Castellani JJ. Orphans Drugs in Development for Rare Diseases. 2011, available at: www.phrma.org/sites/default/files/878/rarediseases2011.pdf

Meeting the Challenge

Rare Diseases and Orphan Drugs

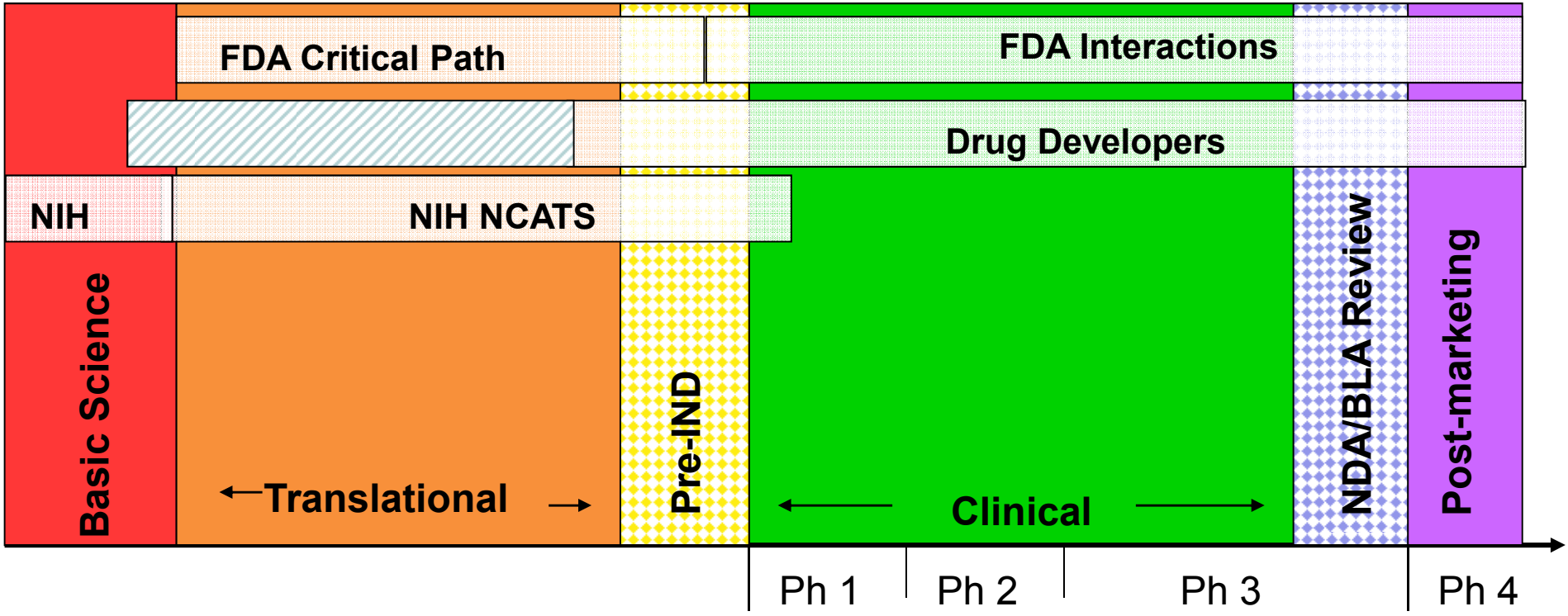
- What is different about rare diseases and Orphan drugs?
  - Diseases are usually poorly or incompletely understood
    - Generally, the lower the prevalence, the less well we tend to understand them
  - Small populations
    - Limited opportunity for study and replication
  - Highly heterogeneous group of disorders
    - 7,000 different diseases
    - Often high phenotypic diversity within individual disorders
  - Usually little precedent for drug development within individual disorders
  - Often requires more (and more careful) planning than non-Orphan
    - Need a solid scientific base upon which to build an overall program

CDER New Molecular Entities & New Biologic Approvals 2011-2012

Disease Precedent ?	
Yes	**No**
2012 (as of May 20, 2012) Respiratory Distress Syndrome in premature infants Gaucher disease	Methotrexate toxicity Cystic Fibrosis *G551D* mutation
2011 Organ rejection, kidney transplant Hodgkins lymphoma Hereditary Angioedema Acute lymphoblastic leukemia Transfusional iron overload Lennox-Gastaut	Advanced melanoma Melanoma *BRAF* mutation Medullary thyroid cancer Anaplastic systemic large cell lymphoma Alk+ non-small cell lung cancer Myelofibrosis

- In same time period for non-rare disease indications: 24 NME/NBs, only 2 did not have disease precedent (8%)

Drug Development – Linear Concept



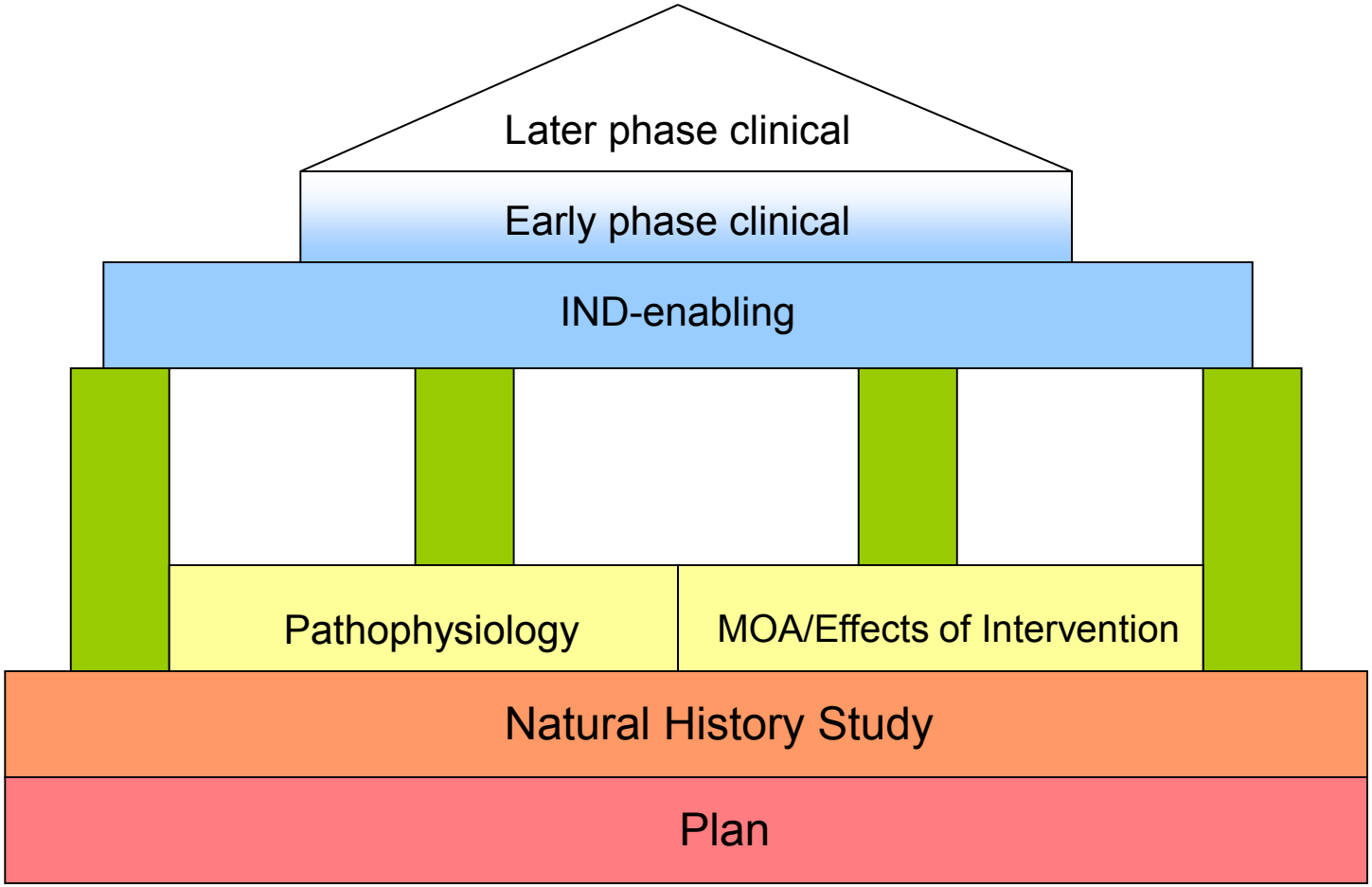
Parallel Concept -- Foundation Building

- •Efficacy trial design
- •Time course
- •Target population
- •COA

- •Pilot COAs
- •Safety

- •Non-clinical P/T
  - •Population
  - •Toxicities
- •Dose exploration
- •Bmkr/COA exploration

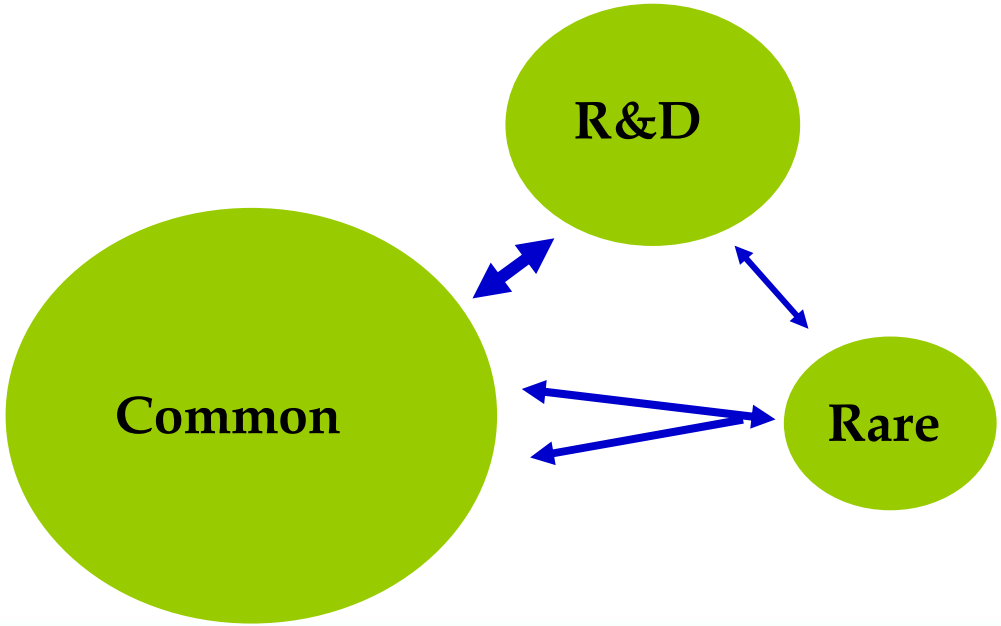
- •Biomarker and COAs ID and development
- •Assays/testing
- •Diagnostics
- •Animal models



Key Points

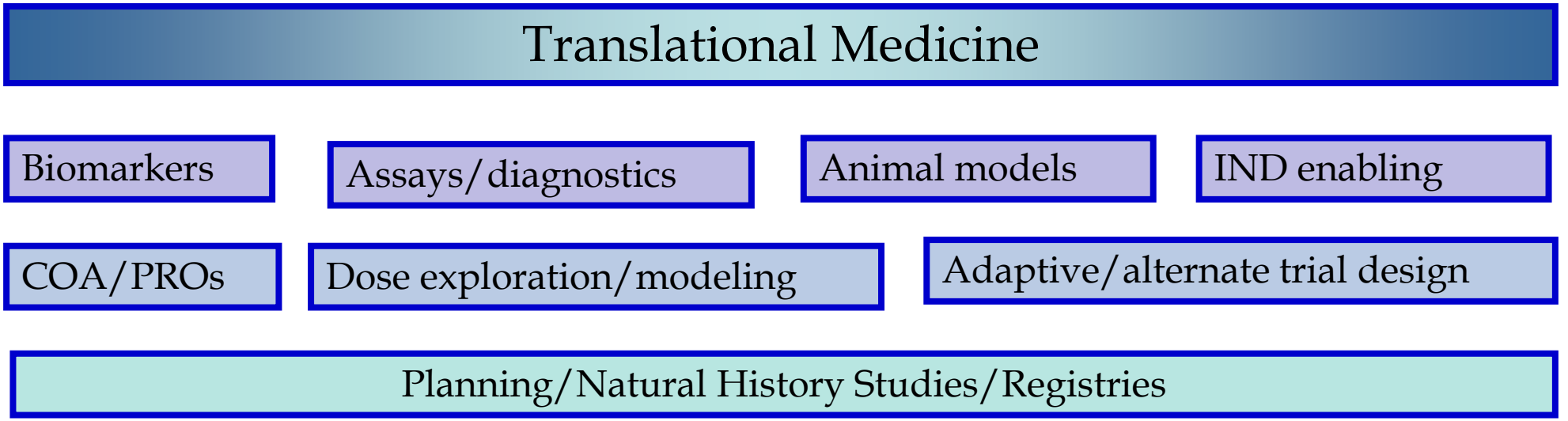
Key Point #1: Rare diseases = Innovation

- Rare diseases have often led the way
  - Science
  - Medicine
  - Product innovation
  - Procedural innovation ("regulatory flexibility")



Key Point #2: Scientific Foundation

- Every indication that Orphans will continue to lead the way – and will increase – in the future
  - Greatest challenge may be in meeting the coming wave, and adapting traditional development plans and "conventional wisdom" to new paradigm
    - Industry, regulatory, academia, researchers, advocacy, payors, etc.



Key Point #3: Disease Diversity

- Monolith (**mon** •*uh* •lith)
  - an obelisk, column, large statue, etc., formed of a single block of stone
  - Something having a uniform, massive, redoubtable, or inflexible quality or character

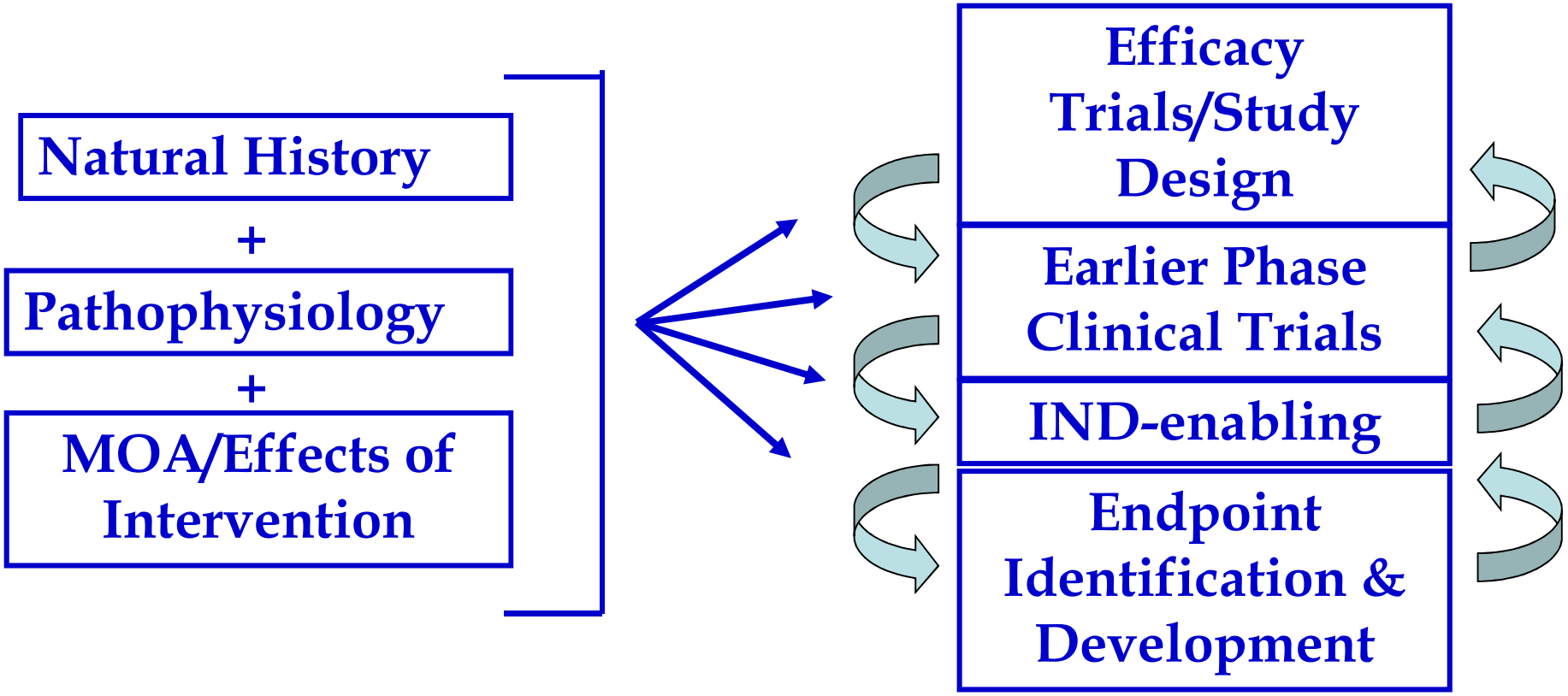
Rare diseases are a highly diverse collection of disorders

-Design and conduct of clinical development programs are highly individualized

-Dependant on disease and population under study, understanding of the intervention and its expected impact on the disease

Key Point #4: Drug Development

- Recommend viewing drug development as a continuum
  - Efficiency ≠ corner-cutting
  - Collaboration, feedback loops, foundation building are essential



Key Point #5: FDA and Rare Diseases

- PDUFA V (proposed) for 2013-2018
  - Increased Rare Diseases Staffing CDER & CBER
  - "Breakthrough" for serious diseases and unmet needs
  - Increased opportunities for interaction between FDA and patients, e.g.,
    - patient-focused drug development
    - benefit-risk assessment framework
  - Staff training
  - Regulatory science development
  - Rare disease evaluation tool

Summary

Rare Disease Innovation	Yes	No
New or different	✓	
First time	✓	
New methods	✓	
Change in anything established	✓	

- Orphan drug development and approvals have produced a major impact on the treatment of both rare and common diseases
- The advent of targeted therapy in orphan diseases is associated with the application of regulatory flexibility and scientific judgment
- As new targeted therapeutics continue to evolve, approvals for orphan drugs will likely continue to grow in importance

Acknowledgements

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