Rare Disease Drug Development: An FDA Perspective

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Orphan Drug Act

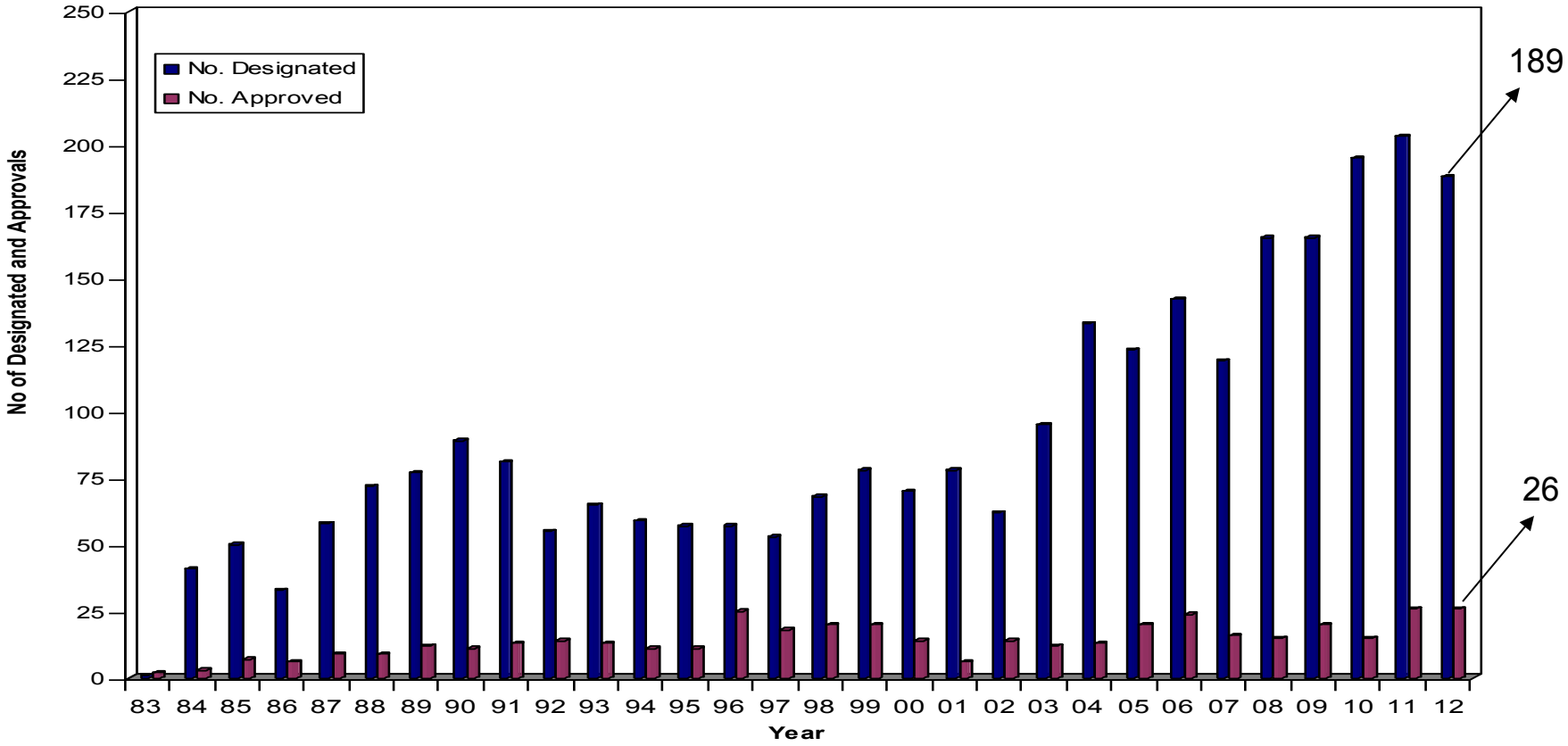
- 1983
- For populations less that 200,000 in the US

- 7 years exclusivity for unpatented compounds
- Tax credits-50% of clinical trial costs
- Research Grants

Orphan Drug Designations/Approvals

Total # of designations through 2012 = 2730

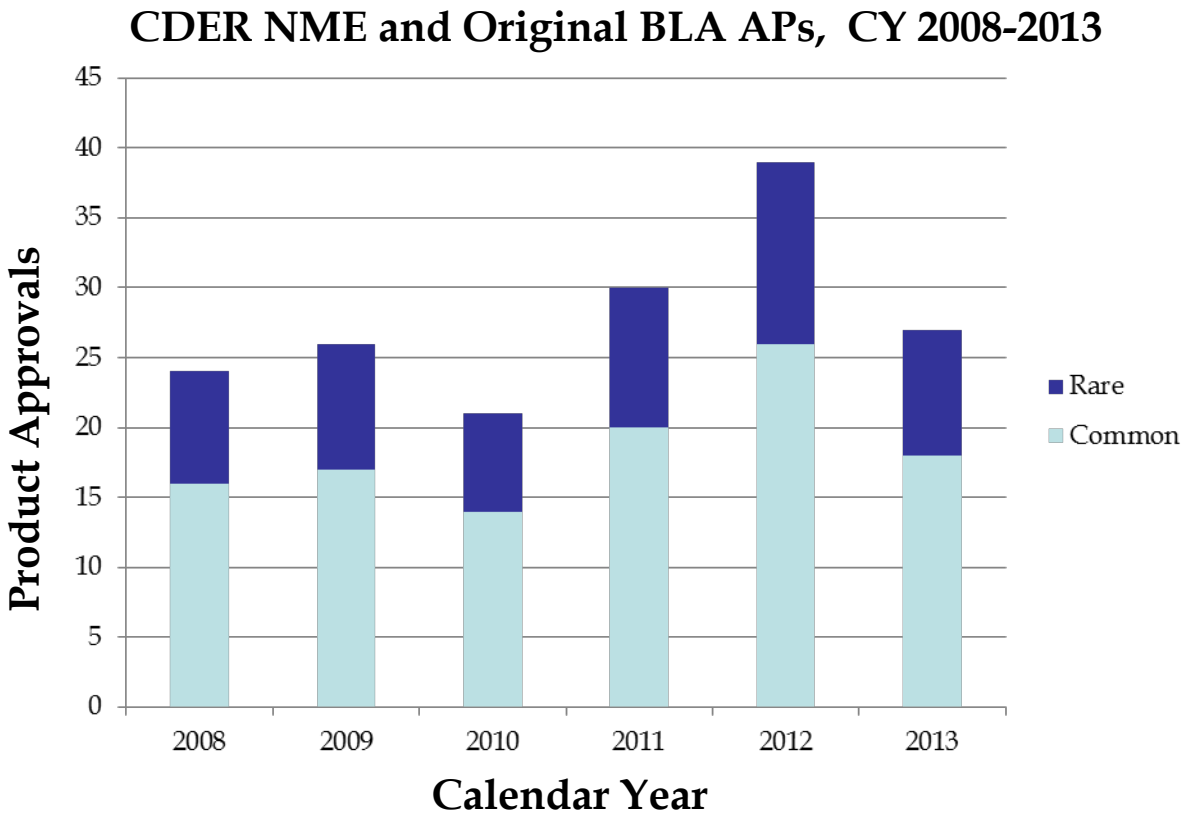
Total # of approvals through 2012 = 421



Courtesy of Gayatri Rao, OOPD

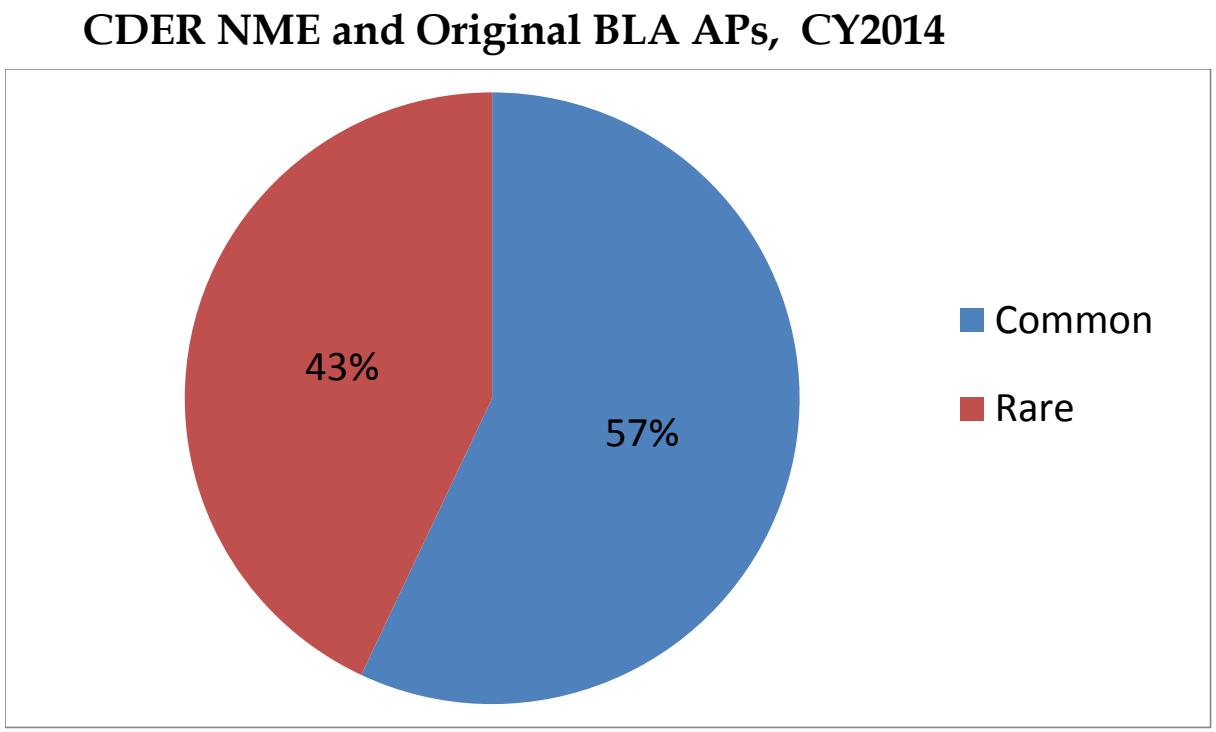
CDER:
Rare Disease Novel Product History

- CY2008-2013* (*as of December 6, 2013)
  - Rare diseases ~1/3 of NME and original biologic APs at CDER



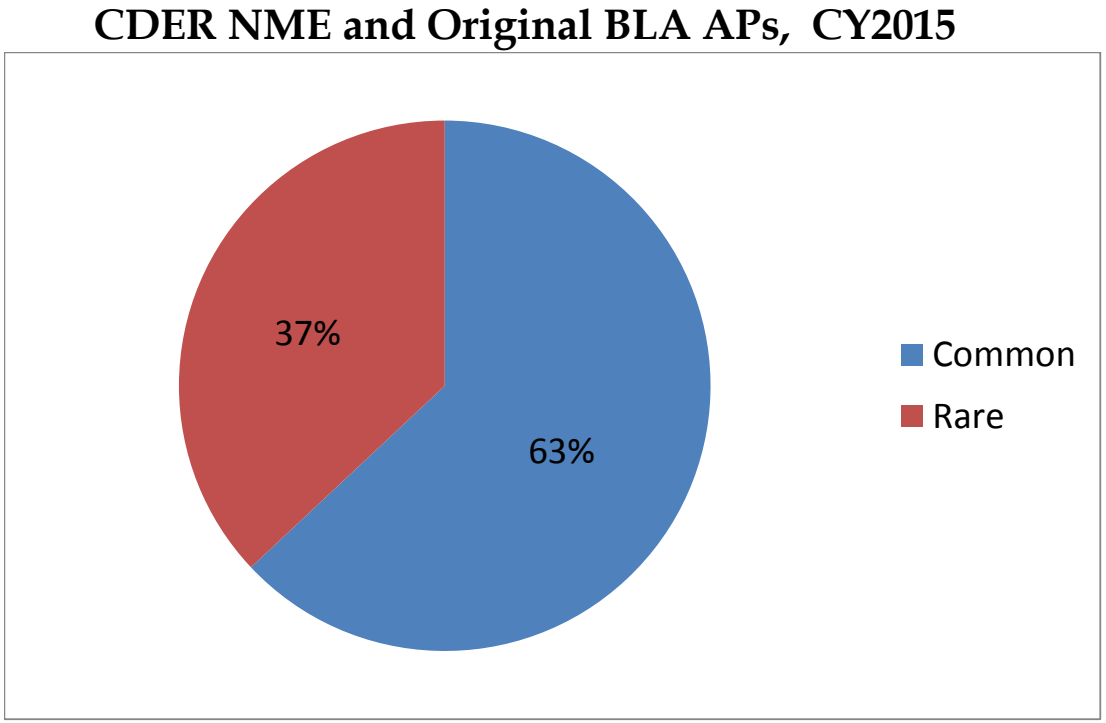
CDER:
Rare Disease Novel Products in 2014

- In CY 2014, rare diseases were >40% of New Molecular Entity (NME) NDAs and original biologics (BLAs) Approvals at CDER in 2014



CDER:
Rare Disease Novel Products in 2015*

- Thus far in CY 2015, rare diseases are ~1/3s of New Molecular Entity (NME) NDAs and original biologics (BLAs) Approvals



*CY2015 thus far includes AP actions taken from Jan 1 through Aug 31, 2015

Expedited Review

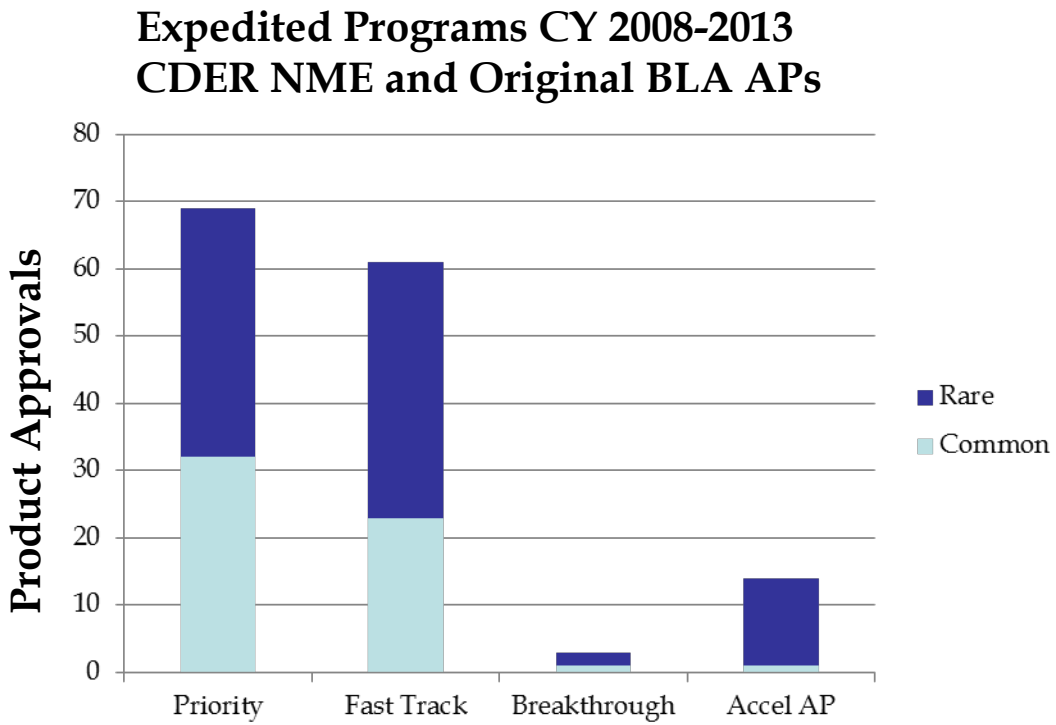
- Draft guidance recently provided for expedited approvals addressing serious diseases with unmet needs (June '13)
  - Fast track
  - Accelerated Approval
  - Priority Review
  - Breakthrough
    - New designation established by FDASIA that expedites the development and review of drugs that—
    - treat serious/life-threatening disease; and
    - preliminary clinical evidence indicates that drug may demonstrate substantial improvement over existing therapies on ≥ 1 clinically significant endpoints

Breakthrough therapy

- Features of breakthrough therapy designation include:
  - Frequent FDA/sponsor communications & meetings
  - Cross-disciplinary project lead assigned to FDA review team to facilitate efficient review and serve as the scientific liaison
  - Organizational commitment involving FDA senior managers and experienced FDA review staff in a proactive collaborative, cross-disciplinary review
- Since its inception in 2012, CDER and CBER have designated 86 new therapies as breakthrough therapies from almost 300 requests
  - 24 have received marketing approval as of April 17
  - About 1/3 have involved rare diseases

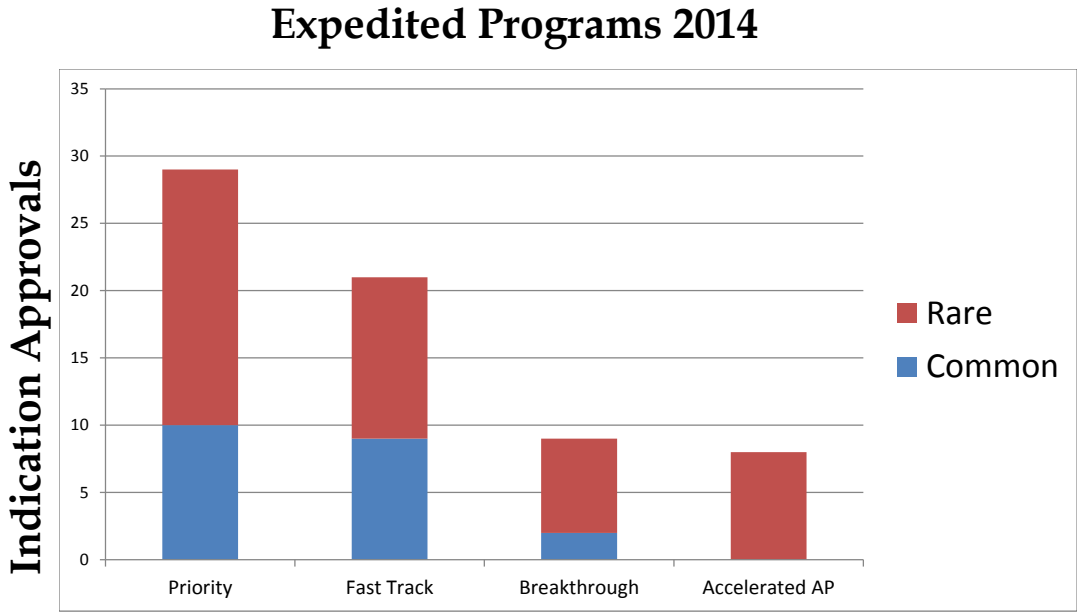
CDER: Expedited Programs

- Rare Diseases
  - Most are serious or life-threatening, unmet medical needs
  - Most qualify for at least one expedited program
    - Many qualify for >1 (almost all for incentives)
    - Rare>>common diseases for expedited programs



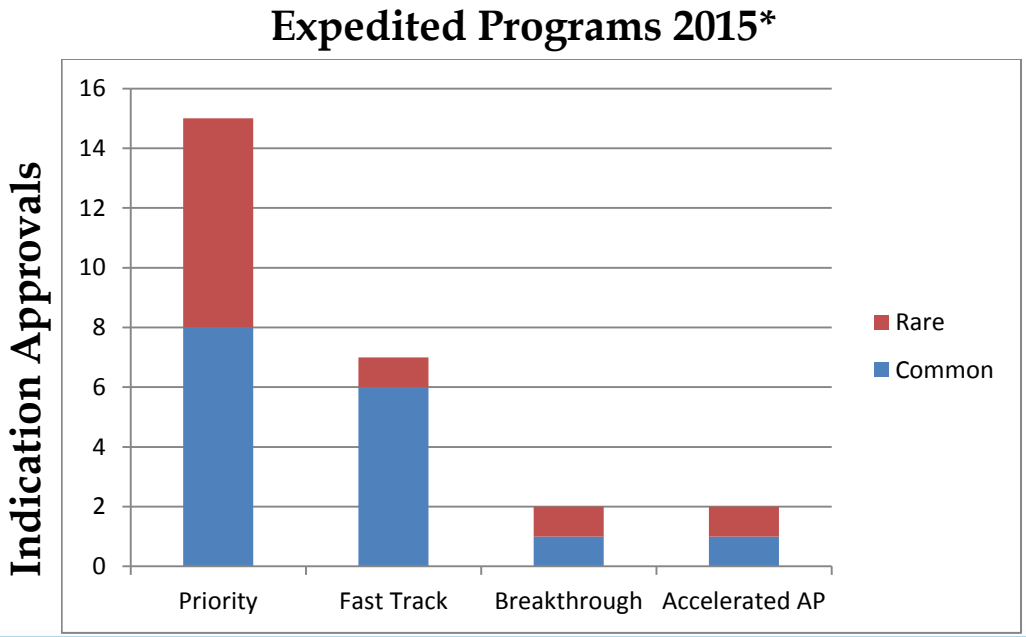
CDER: Expedited Programs

- Rare Diseases 2014, for AP'd NME NDAs/BLAs
  - Most are serious or life-threatening, unmet medical needs
  - In 2014, 100% qualified for at least one expedited program
    - Most qualified for >1 expedited program (85%)
    - Rare>>common diseases for expedited programs
  - 100% qualified for Orphan designation



CDER: Expedited Programs

- Rare Diseases 2015*, for AP'd NME NDAs/BLAs
  - Most are serious or life-threatening, unmet medical needs
  - Thus far in 2015, 7/10 have qualified for at least one expedited program
    - 70% of Rare vs. 47% of common diseases qualified for an expedited program
  - 9/10 were Orphan drug designated products



Targeted APs Trending Up Over Time

CDER Targeted Therapy NME/BLA Approvals

	Targeted Therapies, % of Total		
Year	All	Rare	Common
1990-1992	~8%	~30%	~2%
2000-2002	~10%	~45%	~5%
2010-2014	~25%	~45%	~12%

Targeted Therapies

- Targeted therapies have grown from 5% of new drug approvals in the 1990s to 45% in 2013.
  - 80% of breakthrough and about 60 % of orphan drugs in recent years have also used targeting. 44% of recently approved orphan products
  - Working closely with companies with targeted therapy programs reduced development time by 2 years.
- Common disease subsets ◊ "orphan subsets"1
  - E.g., BRAF V600 mutation subsets of melanoma
- Rare Diseases and Rare Disease subsets
  - E.g., Cystic Fibrosis G551D mutation subset
- Smaller subsets available for clinical trials, smaller clinical development programs
  - Larger magnitude of effects anticipated
  - Safety, R-B assessments

"Patient-focused" Drug Development

- We understand that people with chronic diseases are "experts" in that disease, as far as the symptoms and the impact on QOL, and what might be acceptable tradeoffs
  - On risk
  - On uncertainty
- Series of 20 patient-focused meetings agreed to under PDUFA V
- FDA continuing to develop B/R assessment framework that incorporates burden of disease (hopefully with patient input)
- These are going well, but it is clear that these initiatives reflect a broader trend that is gaining traction
- Question arises over next steps

"Patient-focused" Drug Development

- How to meaningfully collect that knowledge, in rigorous manner, given that there is a spectrum of opinions and and a spectrum of disease burden in any given disease?
- How to do this for the many thousands of diseases?
- Many patient groups and non-profits getting involved in evaluating these issues
- Piloting, e.g., with PRO qualification process and with submission of draft guidances by patient/professional groups
- For FDA/CDER, we must assess how such input can be translated into acceptable endpoints and drug development guidance

How Does FDA "view orphan diseases"

- Is the bar different for efficacy?
  - Yes and no, standards must be present to demonstrate the drug is safe and efficacious in adequate and well controlled trials but the agency has demonstrated tremendous flexibility.
- Functional vs "hard" (survival) endpoints
  - Both acceptable if clinically meaningful and a difference is clearly demonstrable due to therapy. Intermediate clinical endpoints can be used in accelerated approvals as well as qualified surrogate markers likely to predict clinical benefit
- Label "expansion" when the disease has different subpopulations
  - It depends but open to broad label under some circumstances
- Can natural history be used as a control
  - Yes, if collected rigorously in a truly comparable population with a well demarcated endpoint or "hard" endpoint and a major undeniable difference is identified.

CDER: Flexibility

- Level-of-Evidence supporting initial marketing application approval
- Categories
  - ≥2 adequate and well-controlled (A &WC)trials
  - 1 A & WC trial + supporting evidence
  - Other (e.g., case series)

CDER 2014 NME/BLA Approvals

Level-of-Evidence	Rare n (%)	Common n (%)
≥2 A & WC trials	4 (20)	20 (74)
1 A & WC trial + supporting evidence	15 (75)	7 (26)
Other	1 (5)	0

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  - Other (e.g., case series)

CDER 2015* NME/BLA Approvals

Level-of-Evidence	Rare n (%)	Common n (%)
≥2 A & WC trials	1 (10)	8 (47)
1 A & WC trial + supporting evidence	8 (80)	7 (41)
Other	1 (10)	2 (12)

Pediatric Rare Disease Voucher Program

- FDASIA
- FDA will award priority review voucher to sponsors of rare pediatric disease product application that meet certain criteria
  - Prevelance predominently pediatric
  - New drug
  - Not seeking adult indication
- Can seek designation during development
- Voucher is transferable
- Formal guidance to be published

Rare Pediatric Disease Priority Review Vouchers

- 4 RPD PRVs have been awarded
  - Elosulfase (Vimizim) for Morquio A Syndrome (MPS IVa)
  - Dinutuximab (Unituxin) for high-risk neuroblastoma
  - Cholic acid (Cholbam) for bile acid synthesis disorders
  - Uridine triacetate (Xuriden) for hereditory orotic aciduria
- Program sunsets 1 year after third voucher awarded
  - Triggered March 17, 2015
  - Can award RPD PRVs through March 16, 2016
  - GAO report on the program being conducted
- Three sold and one redeemed,

Regulatory Collaborations

- Enhanced international collaborations in recent years
- EU:
  - International Rare Disease research Consortium (IRDIRC)
    - Several FDA members participate
  - Harmonized orphan drug designation application form
  - Regular meetings on orphan drugs, cancer, and pediatrics

- NIH
  - CDER-NIH CC taskforce
  - IND regulatory training workshop

Summary

- More therapies for Orphan diseases approved in 2014 than ever before, a strong trend continues
- Drug Development for Orphan diseases uses expedited review to a great degree
- Targeted Medicines are increasing and are common among therapies for Orphan diseases with both advantages and challenges
- Patient centered drug development is important in orphan disease
- FDA is willing to be very flexible in its approach to serious rare diseases with unmet need
- Rare disease voucher can be valuable incentives
- There is an increased level of global collaboration on rare diseases