

CDER 2016 Update for Rare Diseases

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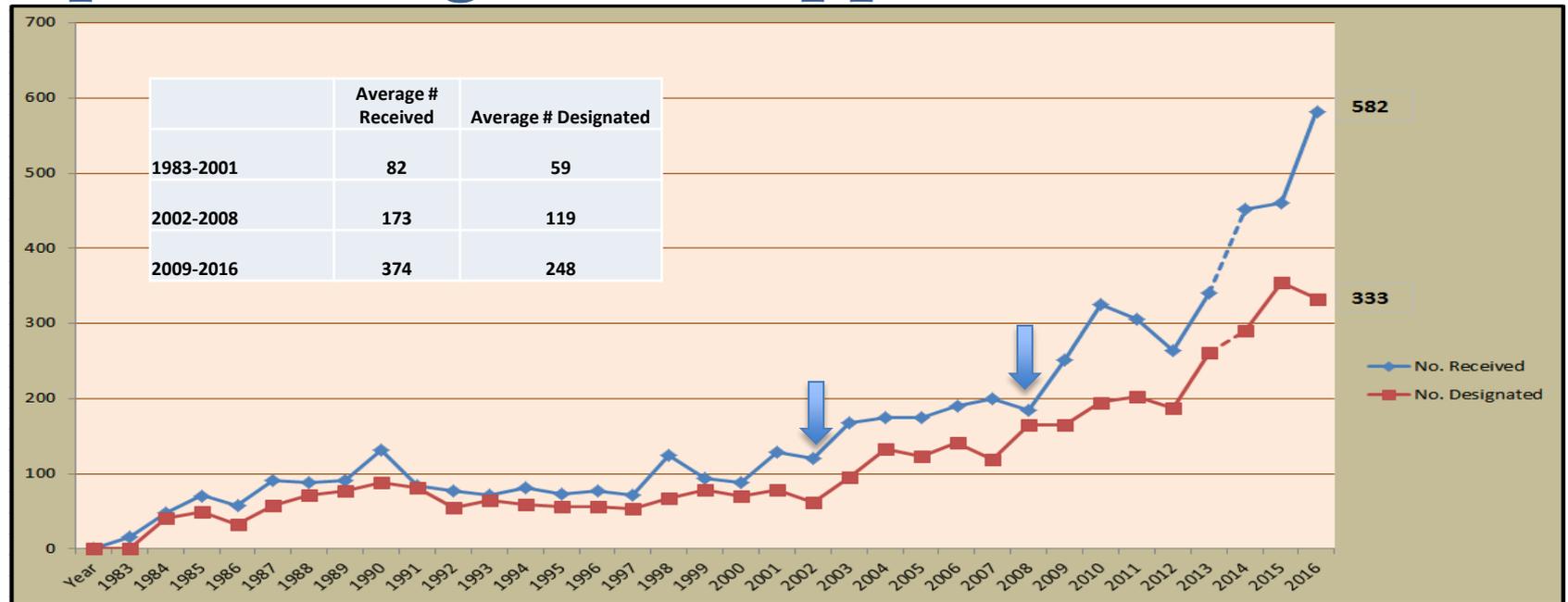
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Challenges for Rare Disease Drug Development



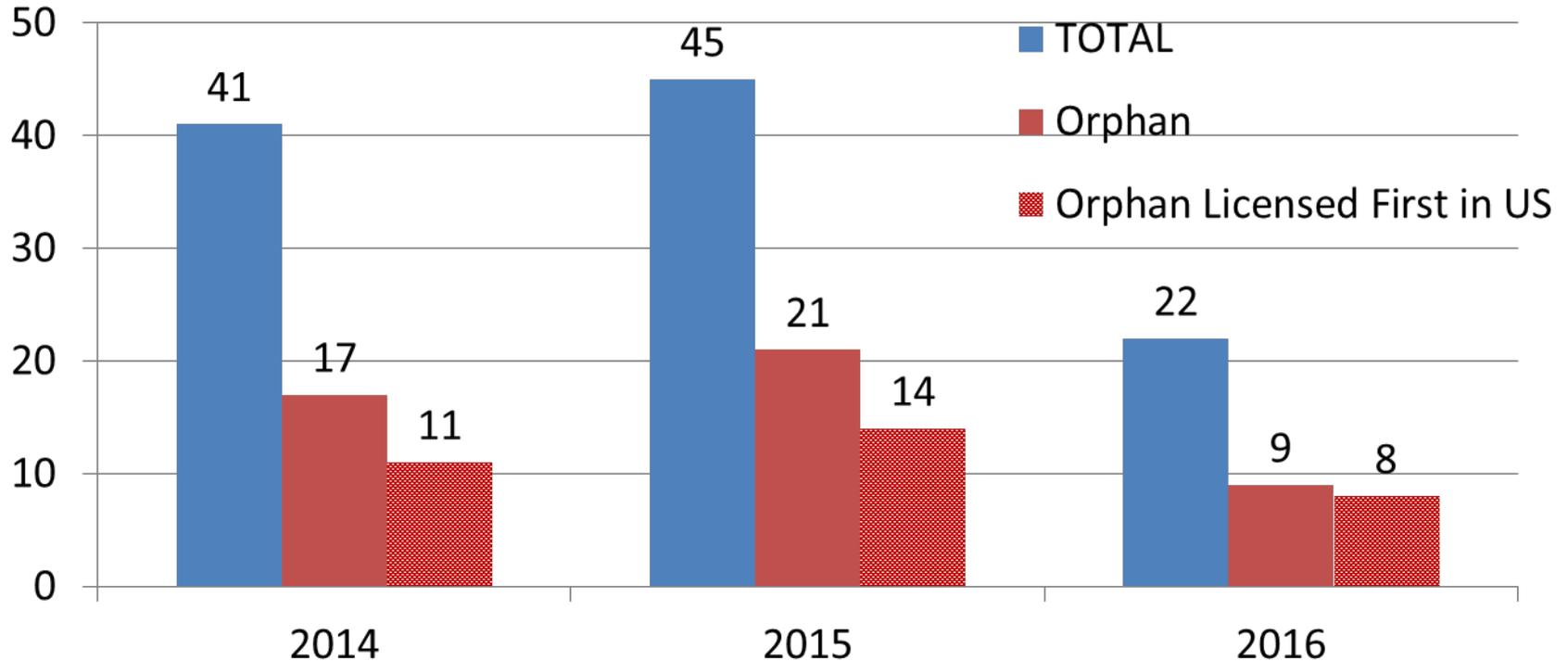
- Rare diseases **natural history** is often poorly understood/characterized
- Diseases tend to be progressive, **serious**, life-limiting and life-threatening and lack **approved therapy**
- **Small populations** often restrict study design and replication and use of usual **inferential statistics**
- **Phenotypic** diversity within a disorder adds to complexity, as do **genetic subsets**
- Well defined and validated **endpoints, outcome measures/tools**, and **biomarkers** are often lacking
- Lack of **precedent** for drug development
- **Ethical** considerations for children in clinical trials

Predicting the Future of Rare Disease Drug Development: Orphan Designation Applications



- Orphan Drug Approvals now greater than 40% of approvals for new molecular entities in 2015 and 2016.

CDER Novel Orphan Drug Approvals CY 2014 -2016*



* as of 31 December 2016

Expediting Rare Diseases Drug Development

- Programs have been developed to target serious diseases with unmet medical needs when a new treatment could provide meaningful clinical benefit

CDER Ensures That Novel Drugs Receive Expedited Review

- 73% of new drug approvals in 2016 used an expedited pathway
 - More than half (68%) of the novel drugs approved to date in CY15 were approved under **Priority Review**
 - About one-third (36%) of novel drugs approved to date in CY15 received **Fast Track** designation
 - 27% were **Accelerated Approvals**
 - 32% were **Breakthrough** designated products

Evaluation of Breakthrough Therapy Designation Program

- Pace of submissions and designations continues strong
- Evaluation as of December 31, 2016
 - Received 412 requests for breakthrough therapy designation
 - CDER granted 144: Hem Onc and antivirals lead but orphan diseases also common
 - 59 original/supplemental applications approved
 - 199 denied, 8 rescinded

Impact of Breakthrough Designation

- Friends of Cancer Research
 - Review time approximately 3 months faster
 - Development time 2.2 years less
 - Greater use of phase 1:2 data
 - Greater use of accelerated approval
- FDA internal analyses
 - Approximately 3 years less development time
 - Review times about 1-2 months less



Expedited Clinical Development Programs

CDER NME approvals 2008-2016

Expedited Programs	Number Rare (n = 113)	Number Non-Rare (n = 195)
Priority Review	87 (77%)	59 (30%)
Fast Track	62 (55%)	43 (22%)
Accelerated Approval	31 (27%)	3 (2%)
Breakthrough Therapy	22 (19%)	8 (4%)
Used any Expedited Program	98 (87%)	69 (35%)

Expedited Clinical Development Programs

CDER NME approvals 2008-2016

EXPEDITED PROGRAMS	Breakthrough N=30	Fast Track N=105	Priority N=146	Accelerated Approval N=34
RARE (N = 113)	19%	55%	77%	27%
Oncology	28%	58%	84%	48%
Non-Oncology	13%	52%	71%	11%
NON-RARE (N = 195)	4%	22%	30%	2%
Oncology	11%	42%	68%	11%
Non-Oncology	3%	20%	26%	1%

Application of Flexible Clinical Development Programs

CDER NME approvals 2008-2016

Flexible Development Programs	Rare Approvals	Non-Rare Approvals
Use of ≥ 1 flexible development approaches*	88 (78%)	68 (35%)
Traditional development program**	25 (22%)	127 (65%)

*Flexible Development approaches are defined as approval supported by other than 2 AWC Studies and/or use of a novel end point

**Traditional Development defined as ≥ 2 AWC studies using endpoints with prior precedents

Flexible Clinical Development Programs

CDER NME approvals 2008-2016

NOVEL ENDPOINTS	Yes N=38	No N=270
RARE, n=113	22%	78%
Oncology	2%	98%
Non-Oncology	44%	56%
NON-RARE, N=195	7%	93%
Oncology	0%	100%
Non-Oncology	7%	93%

“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
- Have had >20 of 24 PFDD meetings, more to go, reports generated
- 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?
- Working with multiple patient organizations who are pioneering patient-focused guidance development for their disease of focus

Expanded Access Programs at FDA

- Use of an investigational drug or biologic to **treat** a patient with a serious or immediately life threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
 - For an investigational drug in a clinical trial, the primary intent is **research**
- There are three types of access:
 - Individual patients (21CFR312.310)
 - Intermediate size population (21CFR312.315)
 - Treatment IND (21 CFR312.320)



Expanded Access Programs at FDA

Submissions and Protocols

- Of 7291 submissions and Protocols from FY 2010 - 2015
 - 99.5% were allowed to proceed
- 97.3% of expanded access submissions were for single patient protocols or single patient emergency protocols

Safeguards for Participants

- Informed consent
- IRB review
- Reporting requirements

Expanded Access: Improving the Regulatory Process

- Adverse events in EA do not derail clinical development
 - In 10,000 INDs only 2 temporary clinical holds due EA AE
- Laborious and somewhat complex process in past.
- This year new simplified form (3926)
 - Estimated time 45 minutes
- 3 new Guidances,
 - Questions and Answers; Charging for Investigational Drugs Under an IND;
 - Individual Patient Expanded Access Applications: Form FDA 3926 final guidance
- Navigating a complex landscape in expanded access

Targeted Therapies

- Targeted therapies have grown from 5% of new drug approvals in the 1990s to 45% in 2013.
 - 80% of breakthrough designations and about 44% of recently approved orphan products
- 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

Targeted APs Trending Up Over Time

CDER Targeted Therapy NME/BLA Approvals

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

Rare Diseases Program in CDER

- Established in 2010
 - Located within the Center for Drug Evaluation and Research (CDER) in the Office of New Drugs (OND) Immediate Office
 - Associate Director for Rare Diseases (ADRD) was the first position created
- Reports to Director of the Office of New Drugs
- Staffing

Rare Diseases Program Projects

Coordinate development of CDER Policies, Procedures and Training

- Several guidances under development
- Continuing involvement with Senior FDA staff re: Rare Diseases Program
- Review Rare Pediatric Disease Priority Review Voucher requests and developed procedures for review and administration

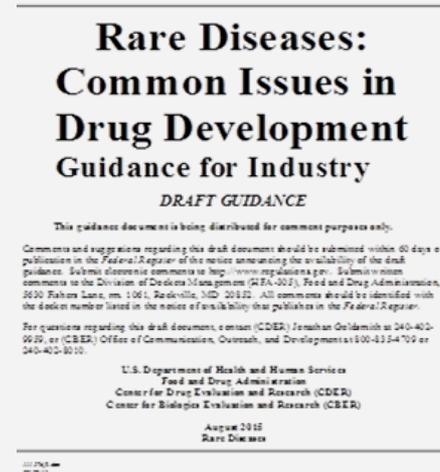
Assist in development of good science

- Regulatory database adjudication committee for NMEs
- Specific projects/peer reviewed publications

Rare Diseases: Common Issues in Drug Development

August 2015 (Draft Guidance)

- To assist sponsors of drug and biological products intended to treat or prevent rare diseases
- To help sponsors conduct more efficient and successful development programs

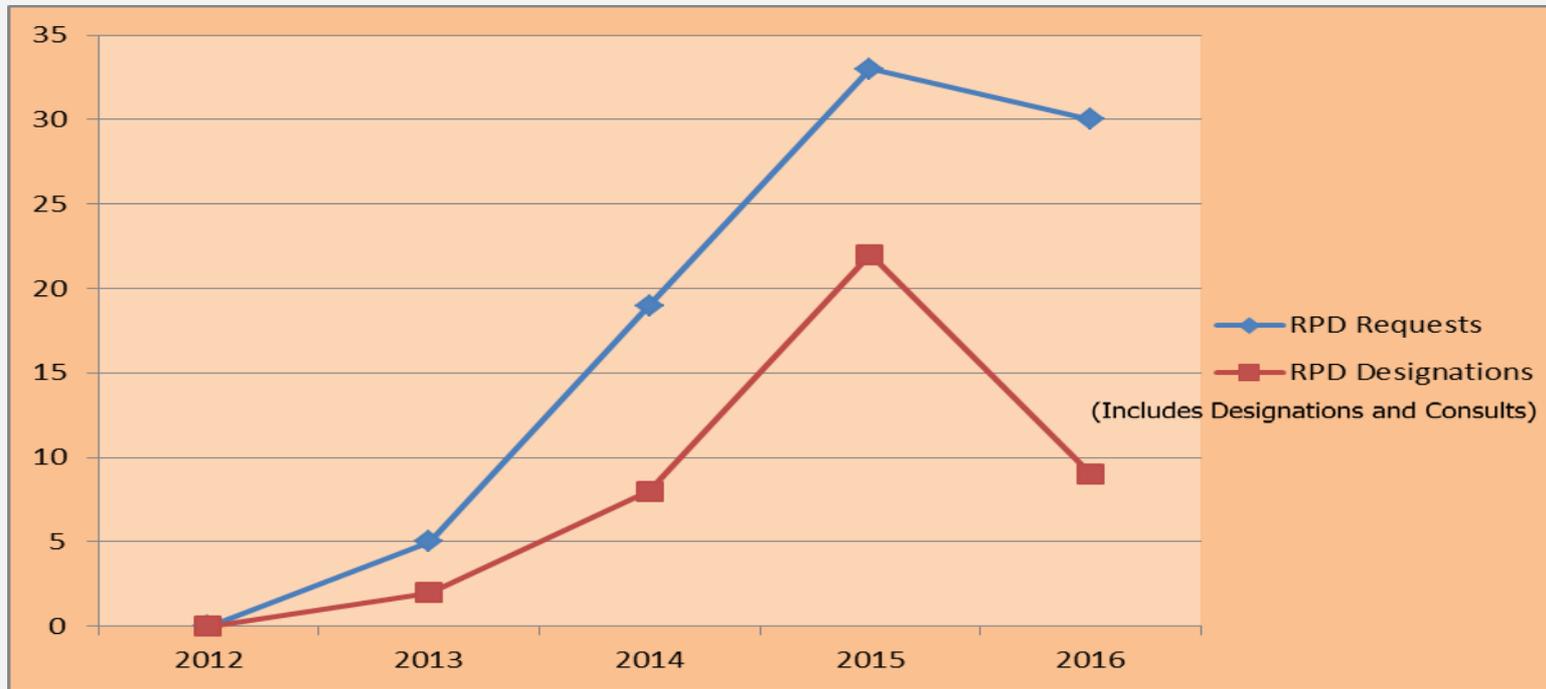


Rare Pediatric Disease (RPD) Priority Review Voucher Program

- 2012 FDA Safety and Innovation Act (FDASIA) [Section 908]
 - Provides an incentive to encourage the development of drugs and biologics for rare pediatric diseases
- Upon approval, the sponsor may be issued a voucher redeemable for a priority review for a *subsequent* application that may not have otherwise qualified for a priority review
- The incentive offers a shorter review clock for marketing applications, 6 months compared with the 10 months standard review time

Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>

RPD Requests and Determinations



Data as of September 15, 2016

Rare Pediatric Disease Priority Review Voucher Program



- The OOPD reviews requests for Rare Pediatric Disease designation
 - 41 Designated/6 Denied/7 Under Review
- Voucher requests are managed by the OND RDP
 - 11 Voucher requests were submitted with an NDA or BLA
 - 7 Vouchers awarded, 3 denied and 1 pending review
 - Two PRV's have been redeemed
- Future (?)
 - Sunsets - 30 September 2016 although pending legislation may be extended to 31 December 2022 (for designation)/31 December 2027 (for redemption)

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
 - New Rare Disease Cluster with EMA
- NIH
 - CDER-NIH CC taskforce
 - IND regulatory training workshop

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.

Important Lessons Learned in Rare Disease Drug Development

- Early natural history studies are invaluable
 - Best if protocol driven, rigorous, consistent objective endpoints
- Better translational development
 - Biomarker assays SHOULD be qualified before clinical studies begin if they are to be seriously considered.
- Need to consider randomization and placebo controls from the very beginning of clinical studies when equipoise clearly exists

Summary

- More therapies for Orphan diseases approved in 2015 than ever before, a strong trend continues (47% (n=21))
- 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
- Recent experience has taught us very valuable lessons regarding natural history, early robust assay development, and randomization from the beginning of clinical studies
- Rare disease voucher can be valuable incentives
- There is an increased level of global collaboration on rare diseases