Rare Diseases and FDA: Perspectives from the Office of Orphan Products Development (OOPD)

Katherine Needleman, MS, PhD, RAC
Director, Orphan Products Grants Program
FDA/OOPD

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Outline

• Background
  – FDA and its Organization in relationship to rare diseases
  – ODA

• OOPD
  – Orphan Drug Designation Program
  – Humanitarian Use Device Designation Program
  – Pediatric Devices Consortia Grants Program
  – Orphan Products Grants Program

• Challenges for Rare Disease Product Development and Working Through those Challenges
  – Regulations/Laws/Flexibility
  – New things on the Horizon – FDASIA
  – Collaborations
  – Meeting with FDA
The U.S. Orphan Drug Act Signed in 1983

Established the public policy that the Federal Government could/would assist in the development of treatment for rare diseases
What is an Orphan Drug?  
U.S. Definition

An orphan drug is defined in the 1984 amendments of the U.S. Orphan Drug Act as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the U.S. Food & Drug Administration.
Orphan Diseases

- ‘Rare’ defined as prevalence of <200,000 in the U.S.
- Includes over 6,000 rare diseases
- Collectively affects approximately 25 million Americans
- Frequently serious/life threatening
The Mission of The Office of Orphan Products Development

To assist and encourage the identification, development, and availability of safe and effective products for people with rare diseases/disorders.
How does OOPD serve its Mission?

• Conducts scientific and regulatory review of orphan product and humanitarian use device designation requests

• Serves as liaison for medical product companies, FDA review divisions, patient advocacy groups, and other government agencies. Provides patients, health care providers and drug sponsors with information regarding the orphan products program and about the FDA review and approval process

• Awards and administers grants to defray orphan product clinical study costs
OOPD Programs

- Orphan Drug Designation Program
- Humanitarian Use Device Designation Program
- Pediatric Devices Consortia Grants Program
- Orphan Products Grants Program
Orphan Product Designation
Orphan Drug Designation Program

• Intended to promote the development of drugs and biologics for rare diseases

• Drug/biologic may be “designated” as an “orphan drug” if it is to prevent, treat, or diagnose a disease/condition that occurs in <200,000 patients in U.S.

• Incentives associated with designation:
  – Tax Credits – 50% tax credit for clinical research and testing expenses
  – Waiver of User Fees – In FY 2013 ~$1.9 M per application, which would otherwise be paid to FDA whether their product is approved or not
  – 7 years of marketing exclusivity upon FDA approval of a specific orphan drug for a specific indication
Process

Office of the Commissioner
OC

Office of Special Medical Programs
OSMP

Office of Orphan Products Development
OOPD

Office of Orphan Products Development
OOPD

Step 1: Orphan Drug Designation

Step 2: Marketing Application - NDA / BLA

Step 3: Orphan Drug Exclusivity

Center for Drug Evaluation and Research
CDER

Center for Biologics Evaluation and Research
CBER

For Complete FDA Organizational Chart see:
Approx Total # Designation requests submitted through 2012 = > 3900
Approx Total # of Designations through 2012 = > 2700
Approx Total # of approvals of orphan designated products through 2012 = >420
Humanitarian Use Devices (HUD)
Humanitarian Use Devices (HUDs)

• Intended to promote the development of devices for rare diseases

• Definition of “HUD”
  – Device used to prevent, treat, or diagnose a disease or condition affecting <4,000 individuals in US per year

• If designated as a “HUD,” can qualify to enter the market through the “HDE” pathway
  – “HDE” = Humanitarian Device Exemption Pathway
  – Safety and Probable Benefit
  – Exemption from the effectiveness standard
    • Restriction on profit (FDAAA 2007/FDASIA 2012)
    • Device to be used with facility IRB approval
    • No comparable device marketed
For Complete FDA Organizational Chart see:
http://www.fda.gov/downloads/AboutFDA/AbouttheFDA/UCM288864.pdf
Pediatric Devices Consortia Grants Program
Pediatric Devices Consortia Grants Program

- Support development of consortia to promote pediatric device development
- Consortia currently funded:
  - University of Michigan MPED & PMDI Pediatric Medical Device Consortium
  - University of California, San Francisco Pediatric Device Consortium
  - Atlanta Pediatric Device Consortium
- Re-authorized for $5.25 million/year for next 5 years
  - Funded over $11 million since 2009
- New RFA was issued; Receipt date in June 2013
Orphan Products
Grants Program
Orphan Products Grants Program

- ~ $14 million annual budget to fund clinical development of products for rare diseases
  - For Phase 1 Studies:
    - Up to $200,000 per year for up to 3 years
  - For Phase 2 and 3 Studies:
    - Up to $400,000 per year for up to 4 years

- Success of the program:
  - > 40 products partially funded by OOPD grants approved for marketing
  - 2 out of the 26 approved orphan drugs from 2012 received OPD funds
    - Kalydeco (ivacaftor) for cystic fibrosis
    - Juxtapid (lomitapide) for homozygous familial hypercholesterolemia

- Next New Application receipt date: February 5, 2014
Generally, receive ~100 applications/year and fund 10-15 new grants/year (~15% success)

For a list of past and currently funded grants:
http://www.accessdata.fda.gov/scripts/opdlisting/oopdgrants/
Products Supported by OPD Grants

(Excludes “no-cost extension” and supplemental grants)
Challenges for Rare Disease Product Development and Working Through Those Challenges
Challenges to Overcome in Developing Rare Disease Treatments

- Populations are small, often exceptionally so
  - Patient Accrual/Geographic Dispersion of Patients/Statistical Significance
- Natural history often incompletely understood
- Robust endpoints, measures, biomarkers lacking
- Large pediatric representation → special trial design and ethical challenges
- Often extraordinary disease burden on patients and families → logistical trial challenges
- Return on Investment vs Cost of Development
Meeting these challenges requires destination-focused strategy

“If a man does not know what port he is steering for, no wind is favorable to him.”

Seneca 4BC-65AD
Understand natural history and pathophysiology

+ Apply knowledge about mechanism of action/expected effect

↓

Develop meaningful endpoints and trial design

↓

Robust, efficient, innovative INDs

↓

Destination: approved drugs
Regulations steer and stabilize

- Maximize the contribution of, and minimize the risk to, patients who volunteer for clinical trials
- Ensure that approved drugs are safe & effective for their intended use

...while providing opportunity to plot a flexible course

Destination ➤ approved drugs for rare diseases
How regulations, legislative acts, and FDA programs helping to plot that course...
What are the regulatory standards for rare disease drug approval?

• Statutory requirements for demonstrating effectiveness and safety are the same for rare and common diseases
• Thus, studies must demonstrate substantial evidence of clinical benefit (21CFR 314.50)
• The statutory requirements *do allow* flexibility in how that demonstration is accomplished
Substantial Evidence of Effectiveness

• Typically two adequate and well-controlled studies for independent substantiation of results
  – An “adequate and well-controlled study” is one that has been designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation” (21CFR314.126)

• However, other pathways are described in Guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”
  – for example, a single study with multiple event measures, pharmacologic/pathophysiologic endpoints, statistically persuasive findings
Flexibility:
NDA Regulations: 21 CFR 314.105

Approval of an Application

“While the statutory standards apply to all drugs...the wide range of uses for those drugs demand flexibility in applying the standards.”

“Thus 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.”
Flexibility:
21CFR 314 Subpart H* (Accelerated Approval)

- Therapy for a serious or life-threatening disease for which there is no FDA-approved “available therapy” may be approved based either on an unvalidated surrogate that is reasonably likely to predict ultimate clinical outcome, or on an outcome other than irreversible morbidity or mortality.

- Post-marketing, the applicant must study the drug further to verify and describe its clinical benefit.

- FDASIA and Accelerated Approval.

*the parallel regulation for biologics is 21CFR Part 601, Subpart E
Regulations steer and stabilize

• Maximize the contribution of, and minimize the risk to, patients who volunteer for clinical trials
• Ensure that approved drugs are safe & effective for their intended use

...while providing opportunity to plot a flexible course

Destination ➔ approved drugs for rare diseases
How regulations, legislative acts, and FDA programs helping to plot that course…

• Orphan Drug Act
  – established policy that federal government would assist in product development for rare disease/condition diagnosis, prevention or treatment

• OOPD
  – Programs and Incentives

• PDUFAs and FDA Acts (FDAMA, FDAAA)
  – Fast Track Designation facilitates development and expedited review of drugs that treat serious diseases and fill an unmet medical need
  – Accelerated approval based on (1) a surrogate reasonably likely to predict clinical benefit or (2) an effect on a clinical endpoint other than survival or irreversible morbidity
  – Priority Review (PDUFA 1992)
    » Fast Track, Accelerated Approval, Priority Review are intended to make therapeutically important drugs available at an earlier time; they do not compromise standards for safety and effectiveness of the drugs that become available through these processes
How regulations, legislative acts, and FDA programs helping to plot that course…

- **CDER Rare Disease Program**
  - Established in Feb 2010 to facilitate and support the research, development, regulation and approval of drug and biologic products for the treatment of rare disorders
  - Coordinate development of CDER policy, procedures and training for review and approval of rare disease treatments
  - Assist in outside development and maintenance of good science for rare diseases
  - Work collaboratively with external and internal rare disease stakeholders to support the development of rare disorder treatments
  - CDER focal point for rare disease community

- **PDUFA**
PDUFA – Prescription Drug User Fee Act

• PDUFA enacted in 1992

• PDUFA IV/Food and Drug Administration Amendments Act (FDAAA) (2007) focused largely on safety

• **PDUFA V/FDA Safety and Innovation Act (FDASIA):**
  – Authorized in 2012
  – law ensures that FDA will continue to receive a source of stable and consistent funding during fiscal years 2013-2017 that will allow the agency to fulfill its mission to protect and promote public health by helping to bring to market critical new medicines for patients.
  – patient centered
    • factor in risk tolerance of patients with unmet medical needs
    • explore endpoints most important to patients
PDUFA V: 1st legislation since ODA to specifically address rare diseases

- Enhancing Regulatory Science & Expediting Drug Development
  - Initiatives to enhance FDA-Sponsor communication
  - Approaches and methods for the conduct of meta-analysis
  - Advancing the use of biomarkers and pharmacogenomics
  - Advancing the development of patient reported outcomes and other endpoint assessment tools
  - Initiative to advance the development of drugs for rare diseases
    - Funding and programmatic direction for CDER’s Rare Disease Program
FDASIA and PDUFA Performance Goals: Provisions Related to Rare Diseases

- Expedited Approval for Serious or Life-Threatening Diseases/Conditions
  - Accelerated Approval
  - Breakthrough Therapies
- Rare Pediatric Disease Voucher Program
- Patient-Focused Drug Development
- External Experts
- Humanitarian Device Exemptions

Reauthorization of Grants:

1. Orphan Products Grant Program - $30M/year
2. Pediatric Devices Consortia Grant Program - $5.2M/year
Expedited Approval for Serious or Life-Threatening Diseases/Conditions: 

**Accelerated Approval**

- Expands the scope of products that qualify for expedited development and review and the range of endpoints that may be used to gain approval.
- FDA may approve an NDA/BLA for a product for a serious or life-threatening condition: including FT product based on a determination that the product has an effect on a:
  - Surrogate endpoint that is reasonably likely to predict clinical benefit
  OR
  - Clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict effect on irreversible morbidity or mortality or other clinical benefit
- Takes into account severity, rarity, or prevalence, as well as lack of alternative treatments.
Expeditied Approval for Serious or Life-Threatening Diseases/Conditions: Breakthrough Therapy

- Designate drug as a breakthrough therapy if:
  - Intended to treat a serious or life-threatening disease/condition AND
  - Preliminary clinical evidence indicates that drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints

- Submit request for designation with or as an amendment to an IND; 60 day review

- If designated:
  - Eligible for everything Fast Track receives
  - Also get more interactive involvement with review division to help guide efficient yet scientifically appropriate trial design
    - Meetings/development advice
Rare Pediatric Disease Priority Review Vouchers

- Similar to and inspired by the Tropical Disease Priority Review Voucher Program
- Uses priority review vouchers as an incentive to develop drugs and biologics for “rare pediatric diseases” (primarily for individuals aged birth to 18 years)
- Designation provisions to determine if a product qualifies as one for a rare pediatric disease and whether an application qualifies as a rare pediatric disease product application
- On approval, provides a voucher entitling subsequent drug or biologic application to priority review
  - Sponsor may transfer entitlement to voucher
  - Must notify FDA 90 days prior to submission that will use PRV
  - Subject to priority review user fee
Patient-Focused Drug Development

- FDA to conduct 20 meetings on different disease areas to obtain patient perspective on disease severity or unmet medical need
  - Sept. 24, 2012 – Published a preliminary list of nominated disease areas and the criteria used for nomination
    - Included rare diseases (e.g., sickle cell disease, amyloidosis, hereditary angioedema)
  - April 11, 2013 – FR published initial 12 diseases to be addressed in FY 2013-2015
    - Includes: Alpha-1 antitrypsin deficiency, idiopathic pulmonary fibrosis, neurological manifestations of inborn errors of metabolism, Huntington's disease, pulmonary arterial hypertension, sickle cell disease
  - April 25 & 26, 2013 – Bethesda, MD – 1st of 20 meetings on Chronic Fatigue Syndrome and myalgic encephalomyelitis (non-rare)
External Experts

• Use experts for consultation in pre-approval period
  – Example topics may include:
    • Severity of rare diseases
    • Unmet medical need associated with rare diseases
    • Willingness and ability of individuals with a rare disease to participate in clinical trials
    • Assessment of benefits and risks of therapies to treat rare diseases

• FDA to develop and maintain a list of external experts used for consultation
Humanitarian Device Exemption

• **Expands** profit-making ability of HDE Devices to include:
  – Disease **Does Not occur in pediatrics** (ONLY occurs in adults)
  OR
  – Disease occurs in pediatric patients in such numbers that the development of the device for such patients is **impossible, highly impracticable, or unsafe** (Majority Adults)

• Amended provision does not cap the number of devices for which the manufacturer may obtain a profit per year at 4000 devices
Collaborations
FDA-Wide Collaborations

- Rare Disease Council
  - Communicate, coordinate and collaborate rare diseases issues
  - Consists of OOPD, CDER, CBER, CDRH, CFSAN, OHCA
- Patient Communications
  - Responding to individual patient-level questions to planning large-scale educational programs
- Drug Shortage Issues
- FDASIA Implementation
- Outreach
  - Produced a number of workshops (Science of Small Clinical Trials, Pediatric Device Workshop, Orphan Products Designations and Grants)
Inter-Agency and International Collaborations

• Inter-agency Collaborations
  – CMS (Center for Medicare & Medicaid Services)
  – NIH (National Institutes of Health)

• International Collaborations
  – EMA
  – Health Canada
  – IRDiRC
Working with FDA

What is the impact of meetings with FDA?
Meeting Timing

- Pre-IND Meeting
- EOP2 A Meeting
- EOP 2 Meeting
- Pre-NDA/BLA Meeting
- Advisory Committee
- End of Review Conference
- EOP1 Meeting
- Post SPA
- Post-SPA
- Pre-Clinical
- Clinical Development
- Marketing Application Review
- Post-action

Slide Courtesy of Larry Bauer
## Mean Clinical Development Time

### NME & New Biologics Applications

#### 2010-2011

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NMEs and New BLAs
Pre-NDA Meetings v.
Regulatory Actions
2009-2010

Slide Courtesy of Larry Bauer
Characteristics of rare disease marketing applications associated with FDA product approvals 2006-2010*

<table>
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<th>Indication</th>
<th>Approval No. (%)</th>
<th>Non-Approval No. (%)</th>
<th>OR (95% CI)</th>
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<tr>
<td>Rare Disease</td>
<td>36 (77%)</td>
<td>11 (23%)</td>
<td>1.3 (0.6, 3.2)</td>
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<tr>
<td>Common Disease</td>
<td>82 (71%)</td>
<td>33 (29%)</td>
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The approval rates for applications for rare vs. common diseases are very similar

How is all this working for rare diseases?

• ~1/3 of new molecular entity approvals are for rare disease
  www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

• Substantial trial design diversity in applications for rare disease drugs
  – ~2/3 rare disease drug approvals past 3 years based on level of evidence
    other than 2 well-controlled RCT
    A Pariser

• Cataloguing FDA's flexibility in regulating therapies for persons with rare
  disorders – 90/135 (~2/3) non cancer orphan therapies approved as NCE
  classified as FDA used flexibility when determining whether the statutory
  requirement for demonstrating the drug’s effectiveness had been met

• Meetings prove useful for development – shorter development times; more approvals
OOPD Website

- http://www.fda.gov/orphan

Your Link to:

- Overview of FDA Office of Orphan Products Development
- Guidelines for designation application
- List of designated and approved orphan products
- Grant application information
- List of ongoing orphan grant studies
- Contact information for OOPD staff

- Main Telephone # is (301) 796-8660
Contacts

Katherine Needleman
katherine.needleman@fda.hhs.gov

CDER RDP:
Anne Pariser or Larry Bauer
Anne.pariser@fda.hhs.gov
larry.bauer@fda.hhs.gov
Thank You!