Rare Disease Day(s) 2013 & Orphan Drug Development Overview

7 March 2013
Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her working apart from the beaten path. Nor is there any better way to advance the proper practice of medicine than to give our minds to discovery of the unusual law of nature by the careful investigation of cases of rarer forms of disease.

- William Harvey 24 April 1657 -
Rare Disease Overview

- Classified as a disease, disorder, condition affecting > 200,000/territory
- Rare diseases are not rare accumulatively
- Over 7,000 rare diseases exist
- ~30MM people affected in the US
- >250MM people affected worldwide
- 421 drugs approved for rare diseases
- ~250 disease groups represented

High Unmet Medical Need
Renewed Interest in Orphan Drug Development

- RDs present a potential global public health issue driven by increasing scrutiny from media and relentless patient advocacy
- 30th Anniversary of the Orphan Drug Act
- PDUFA V Amendment
- **International Movement**
  - European Commission will provide €144 million of new funding for orphan drug development, announced on 28 February at RDD Conference
    - Expected to impact 30 million Europeans
    - 26 research projects, 300 participants, 29 countries
    - Focus on increased international collaboration
  - Orphan drug development accounts for >11% of total NIH budget
    - NIH Rare Diseases: $3.527 B (~9400 research projects, 2137 rare diseases)
    - NIH Orphan Drugs: $750MM (~1650 research projects)

200 New Therapies by 2020
Important Rare Disease Activities

2012

• Expanded emphasis on patient registries
• Establishment of NCATS (National Center for Advancing Translational Sciences)
• Enactment of FDA Safety and Innovation Act (FDASIA)/PDUFA V
• Expansion of the Undiagnosed Disease Program
• Continual growth in patient advocacy groups
• Focus on global regulatory collaborations (IRDiRC)
• SSA Compassionate Allowance & Quick Determination Fast Track Initiatives
• Creation of a Congressional Rare Disease Caucus

2013

• ICD-11 nomenclature beta testing underway to properly classify rare disease (to address ICD-9 and 10 shortfalls)
• Rare disease clinical research network restructuring (ORDR at NCATS)

Renewed Interest in Rare Diseases/Disorders
NCATS: National Center for Advancing Translational Sciences

- Developed and implemented during 2012; conception began in 2011
  - Director, Christopher P. Austin, MD (neurologist)
- Investigate prevalence of rare diseases
  - Industry may have these answers; NIH and FDA don’t
- Focus on collaborations ("translation is a team sport")
- Consider longer term financial implications
  - Currently, $200-300,000/patient/year is cost of drug and reimbursable to drug company
  - Increase of annual drug costs to further financial incentives
- Capitalize on repurposing opportunities
  - Novel approvals
  - Generic approvals
- Build awareness of scientific opportunities
  - 4,500 rare genetic diseases in 2012; ~50 in 1997
FDASIA/PDUFA V

- Signed into law 9 July 2012
- Funds new activities at FDA FY 2013-2017
  - MDUFA, GDUFA, BSUFA
- Due to extensive public scrutiny on health “crisis” surrounding RDs
- “Advancing Development of Drugs for Rare Diseases”
  - Increase RD staffing
  - Establish FDA training program in collaboration with NORD & NIH clinical center
  - Develop & disseminate guidance
  - Increase scientific presence
  - Establish accountability through tracking and evaluation (RDD database)
  - Creation of Rare Disease Program
    - >45 years FDA experience
    - >30 years NIH experience
    - Diverse backgrounds
IRDiRC: International Rare Disease Research Consortium

- Cooperation at an international level to stimulate, coordinate & maximize output of RDs around the world
- 200 by 2020
- Develop diagnostic tests for all RDs
- Establish scientific committees for RD therapeutic groups
- ~15 members comprised of scientists, patients, industry
- First public meeting 16-17 April
Other Essential Groups in Rare Disease Development

• Disease Advocacy Groups
  – Venture philanthropy
    • Cystic fibrosis is the most successful disease group in the country in terms of new therapeutics
    • MJFF is the best example of group inertia
    • Groups that could learn from these examples: Susan G. Komen & Avon Foundations

• FDA
  – Progress apparent, however Advisory Committee commissions desperately need refocusing
    • FDA examiners have determined their voting status prior to Committee meetings
    • Much better use of significant talent and resources by utilizing these experts early on in the orphan drug development process

Regulatory Uncertainty is Biggest Obstacle in Development of RDs
Other Essential Groups in Rare Disease Development

- Social Security Administration (Medicare/Medicaid)
  - Implementation of the Quick Determination Fast Track to approve Compassionate Allowance for devastating diseases
    - 200 diseases approved under Compassionate Allowance Program
    - To date all allowances have been orphan drugs
    - Quick Determination Fast Track in days vs months/years
    - Average examiner has 3 years experience
  - Further opportunity for approval under Program driven by ability to stratify specific patient populations by probability of disease progression and severity
Rare Diseases at the FDA: Perspectives from the Office of Orphan Products Development

• 30 year anniversary of the Orphan Drug Act
  – 4 January 1983
  – Increased recognition of the lack of incentives in this field

• Drug Designation Program
  – Drug intended to prevent, treat or diagnose a condition (rare disease) that occurs >200,000 patients in the US
  – Significant tax credits for clinical trial costs: 50% clinical trial cost reimbursement
  – PDUFA fee waiver ($1.9MM)
  – 7 years market exclusivity
  – Recent focus on repurposing of drugs
  – Apply for designation at the animal study stage
  – Forces cross agency interaction
  – 300 requests annually; 200 receive designation

Think Long Term & Think Early About Designation
Rare Diseases at the FDA: Perspectives from the Office of Orphan Products Development

- 2,730 total orphan drug designations through 2012
- 421 total orphan drug approvals through 2012

Disease Groups Receiving ODD

- Oncology (36%)
- Neurology (13%)
- Hematology (7%)
- Pulmonary (6%)
- Metabolism (5%)
- Ophthalmology (5%)
- Other (28%)
Rare Diseases at the FDA: Perspectives from the Office of Orphan Products Development

- Orphan Products Grants Program
  - $14MM annual budget for clinical development
    - Phase I: $200,000/year for up to 3 years
    - Phase II & III: $400,000/year for up to 4 years
  - Two approved orphan drugs from 2012 received funding
    - CF (Kalydeco)
    - Hypercholesterolemia (Juxtapid)
  - Annual submission deadline
  - ~15% success rate of funding
    - ~100 applications/year; ~15 receive funding
    - One dystonia drug received funding (2000; Investigator driven trial at Mount Sinai Medical Center)
Rare Diseases at the FDA: Perspectives from the Office of Orphan Products Development

- FDA-Wide Collaborations
  - Rare Disease Council
    - Composed of representatives from OOPD, CDER, CBER, CDRH, CFSAN, OSHI
  - Patient Communications
    - Individual patient inquiries & large scale educational programs
  - Drug Shortage Issues
  - FDASIA Implementation (PDUFA V)
  - Outreach

- Interagency Collaborations
  - NIH, CMS

- International Collaborations
  - IRDiRC (International Rare Diseases Research Consortium)
  - EMA
  - Health Canada
FDA CDER: Rare Disease Focus

• CDER responsible for ~90% of Orphan Drugs at FDA
  – Remainder at CBER (blood & tissue derived products, stem cells, gene therapy, vaccines)

• Rapidly growing area of drug development
  – ~1/3 of NMEs and NBEs are for RD indications
  – For NBEs specifically, ~2/3 are for RD indications
FDA CDER: Rare Disease Focus

- Drug approvals follow designation trends regarding indications
- 2008-2013
  - 35 oncology drugs approved
  - 9 neurology drugs approved
  - 8 hematology
  - 7 immunology
  - 7 infectious disease
Orphan Drug Application Process: Status Rationale

• Product
  – Disease description
  – Scientific rationale

• Prevalence
  – Low prevalence
  – Potential for return on investment

• Promise
  – No other methods exist in the community
  – Other methods exist but are not considered satisfactory
  – Other satisfactory methods exist but this medicinal product will be of significant benefit to those affected by the condition
Orphan Drug Designation Application

- Cover Letter
- Designation request statement
- Sponsor Information
- Disease description & unmet medical need rationale
- Drug description & scientific rationale
- Similar drug explanation
- Disease subset explanation
- Summary of regulatory & marketing history
- Disease prevalence
- 3rd party requestor explanation
- References
Orphan Designation Application (Sections II.3.2 & II.3.3)

<table>
<thead>
<tr>
<th>II.3.2  Strength(s) and Pharmaceutical form(s) (use current list of standard terms - European Pharmacopoeia)</th>
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<tr>
<td>Strength(s)</td>
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<tr>
<th>II.3.3 Proposed route(s) of administration (use current list of standard terms - European Pharmacopoeia)</th>
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- Dosage Forms
- Patient Friendly (formerly short) Terms
- Routes & Methods of Administration
- Containers, Closure and Delivery Devices
- Combined Terms
# Orphan Drug Designation

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<thead>
<tr>
<th></th>
<th>US FDA</th>
<th>EU EMA</th>
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<tbody>
<tr>
<td>Protocol assistance</td>
<td>Extensive protocol assistance</td>
<td></td>
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<tr>
<td>7 years market exclusivity</td>
<td>10 years market exclusivity</td>
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<tr>
<td>Waived PDUFA costs ($1.9MM)</td>
<td>Fee reductions</td>
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<tr>
<td>Grants available</td>
<td>Grants available</td>
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<tr>
<td>Tax incentives (50% of all clinical trial cost)</td>
<td>Available; country-by-country variability</td>
<td></td>
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<tr>
<td>US specific</td>
<td>Centralized; application covers all countries served by the EMEA</td>
<td></td>
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<tr>
<td>Confidential application; public only if designation granted</td>
<td>Semi-confidential application</td>
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Clinical Trial Comparisons

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<tr>
<th>Study Parameter</th>
<th>Orphan</th>
<th>Non-Orphan</th>
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<tr>
<td>Studies Analyzed</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Number of Patients in Pivotal Trial</td>
<td>96</td>
<td>290</td>
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<tr>
<td>Randomization</td>
<td>30%</td>
<td>80%</td>
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<tr>
<td>Double-blind Study Design</td>
<td>4%</td>
<td>33%</td>
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<tr>
<td>Disease Response as Primary Study Outcome</td>
<td>68%</td>
<td>27%</td>
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<tr>
<td>Survival as Primary Study Outcome</td>
<td>8%</td>
<td>27%</td>
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<tr>
<td>Serious Adverse Events</td>
<td>48%</td>
<td>36%</td>
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**Overall Lower Hurdle for Orphan Drug Clinical Development**
Questions?

For more information or assistance in the development of your orphan drug program contact us at info@theorphangroup.com.
Thank You!

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