Rare Diseases, Orphan Drugs and Innovation: US FDA Perspective

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Innovation

- Innovation (in-uh-vey-shuhn)
  - 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

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

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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\textsubscript{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

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

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

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 PDGFR, 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 \(\rightarrow\) targeted subpopulation
      – E.g., crizotinib for ALK+ non-small cell lung CA
      – vemurafenib for BRAF+ melanoma
    • Rare disease \(\rightarrow\) targeted subpopulation
      – E.g., ivacaftor for Cystic Fibrosis
Recent History -- Level of Evidence

2010-2012 NMEs and New Biologics

Cancer 5 applications
CV 2 applications (~20k patients/each)

Trial size <20 to >1000, median ~250
Substantial trial design diversity
The Coming Wave of Orphan Products
Orphan Designations

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

Orphans by Therapeutic Area 1983-2012

Future Projections/Estimates--Orphan Designated Products

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

<table>
<thead>
<tr>
<th>Disease Precedent?</th>
<th>2012 (as of May 20, 2012)</th>
<th>No</th>
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<tbody>
<tr>
<td>Yes</td>
<td>Respiratory Distress Syndrome in premature infants</td>
<td>Methotrexate toxicity</td>
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<td></td>
<td>Gaucher disease</td>
<td>Cystic Fibrosis G551D mutation</td>
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<td></td>
<td></td>
<td>2011</td>
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<td>Organ rejection, kidney transplant</td>
<td>Advanced melanoma</td>
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<tr>
<td></td>
<td>Hodgkins lymphoma</td>
<td>Melanoma BRAF mutation</td>
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<td></td>
<td>Hereditary Angioedema</td>
<td>Medullary thyroid cancer</td>
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<td></td>
<td>Acute lymphoblastic leukemia</td>
<td>Anaplastic systemic large cell lymphoma</td>
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<tr>
<td></td>
<td>Transfusional iron overload</td>
<td>Alk+ non-small cell lung cancer</td>
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<tr>
<td></td>
<td>Lennox-Gastaut</td>
<td>Myelofibrosis</td>
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- In same time period for non-rare disease indications: 24 NME/NBs, only 2 did not have disease precedent (8%)
Drug Development – Linear Concept

- Basic Science
  - Translational
  - Pre-IND

- Clinical
  - Ph 1
  - Ph 2
  - Ph 3
  - Ph 4

- NDA/BLA Review
- Post-marketing

Involvement of:
- NIH
- NIH NCATS
- FDA Critical Path
- FDA Interactions
- Drug Developers

Interactions with:
- NIH
- FDA Critical Path
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

Later phase clinical

Early phase clinical

IND-enabling

Pathophysiology

MOA/Effects of Intervention

Natural History Study

Plan
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.

Translational Medicine

- Biomarkers
- Assays/diagnostics
- Animal models
- IND enabling
- COA/PROs
- Dose exploration/modeling
- Adaptive/alternate trial design
- Planning/Natural History Studies/Registries
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

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<tr>
<th>Natural History</th>
<th>Efficacy Trials/Study Design</th>
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<tbody>
<tr>
<td>+ Pathophysiology</td>
<td>Earlier Phase Clinical Trials</td>
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<tr>
<td>+ MOA/Effects of Intervention</td>
<td>IND-enabling</td>
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<td>Endpoint Identification &amp; Development</td>
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[Diagram showing the flow of drug development with natural history, pathophysiology, and MOA/Effects of Intervention feeding into efficacy trials and study design, with feedback loops indicating ongoing iterative process.]
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

<table>
<thead>
<tr>
<th>Rare Disease Innovation</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>New or different</td>
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<td>✔</td>
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<tr>
<td>First time</td>
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<td>✔</td>
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<tr>
<td>New methods</td>
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<tr>
<td>Change in anything established</td>
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• 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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