Accelerating Development of Treatments for Rare Diseases

Emil D. Kakkis, M.D., Ph.D.*
President and Founder
Kakkis EveryLife Foundation
Former Chief Medical Officer,
BioMarin Pharmaceutical Inc.

* Dr. Kakkis has financial conflicts of interest related to Aldurazyme and BioMarin
IOM Committee Activity
Accelerating Rare Diseases Research and Orphan Product Development

Project Scope Relevant to Today’s Presentation

- Describe the strengths and limitation of current development pathways for new drugs, medical devices, and biologics for rare diseases (taking into account developments in genetic testing) and discuss the special challenges that rare diseases create for research and product regulation;

- Examine current public policies relevant to product development for rare diseases, including the Orphan Drug Act, the Humanitarian Use Device exemption, the approaches of the National Institutes of Health and the Food and Drug Administration

- Consider, as part of a national policy framework, a wide range of public and private strategies and innovations,
  - revising policies and regulations;
  - encouraging alternative research financing mechanisms
Goals for the CURE THE PROCESS Campaign

• Establish a new Office of Drug Evaluation specifically for Biochemical and Genetic Diseases
  • Specialize the organization for review to narrower focused groups
  • Recruit and retain individuals with the right training/skills
    • New positions to supplement the small existing core of people
    • Improve academic potential and reduce workload of complex diseases

• Improve the accessibility of Accelerated Approval Process (Subpart H)
  • Create qualification criteria for surrogate endpoints in ultra-rare disorders
  • Express this policy in a guidance on the qualification criteria

• Allow alternative more powerful study designs and analyses for clinical endpoint driven pivotal studies
  • Need to accept optimal statistical methods
  • Allow alternate designs for rare heterogeneous diseases
  • Express this policy in the form of a guidance
Our campaign is formally endorsed by 80 disease organizations
Rare disease treatments are being developed but not all orphan diseases benefit

**Successes**
- Many approved drugs

**Challenges**
- Thousands ultra-rare diseases without approved drugs
  - Ceroid lipofuscinoses
  - Methylmalonic acidemia
  - Mannosidosis
  - Mucopolysaccharidosis VII
  - Sanfilippo Syndromes
  - Von Gierke Disease type 1
  - Galactosialidosis
  - Propionic acidemia
  - Wolman Disease
  - Glycogen storage disease type IV
  - Isovaleric acidemia
  - Menkes disease
  - Tay Sachs
Initiation of drug development less likely for ultra-rare disorders


- Extent of orphan drug development quantified by measuring the likelihood of obtaining at least one US or EU orphan designation for a disease
- 588 rare diseases in the dataset
- 3 prevalence classes
- ~0.5, ~5 and ~25 per 100,000
- 64.2% (115/179) more common orphan diseases (had at least one designation)

- Only 32.5% (133 out of 409) of ultra-rare diseases had at least one designation.
Preliminary Results

Orphan Drug Development Trends

Prepared for Kakkis EveryLife Foundation
January 27, 2010

• **Objective:** Assess the extent to which there *may* or *may not* be biases in orphan drug development towards “higher” prevalence orphan diseases
  - US orphan \(\leq 200,000\) (prevalence \(\leq 67/100,000\));
  - **Ultra-rare definition** \(\leq 6,000\) in US (prevalence \(\leq 2/100,000\))

• **Timeframe:** 1997-2009

Orphan drug designations and approvals: All new orphan designations \((n=1,310)\) from 1997-2010 pulled from the FDA Orphan Drug Product designation database\(^1\)

• **83%** of rare diseases \((1,563/1,892)\) are **ultra-rare**

  Determined percentage of “rare” diseases that are “ultra orphan” to contrast to orphan designations: Analysis of Orphanet report series on rare diseases

• Only **11%** of orphan designations were for ultra-rare diseases \((144/1,310\) orphan designations)\(^2\)

Orphan Designations 1997 to 2009

- 1,310 new orphan designations granted from 1997 to 2009*
- 144 were for products addressing “ultra rare” diseases
  - This equates to 11% of all orphan designations
- Overall number of designations per year increased substantially over the timeframe
- There is no significant trend in the annual percentage addressing ultra rare diseases

* As of November 15, 2009

<table>
<thead>
<tr>
<th>Year</th>
<th>All Orphan Designations</th>
<th>Ultra Rare Designations</th>
<th>Ultra Rare %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>51</td>
<td>8</td>
<td>16%</td>
</tr>
<tr>
<td>1998</td>
<td>68</td>
<td>9</td>
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<tr>
<td>2002</td>
<td>61</td>
<td>3</td>
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<tr>
<td>2003</td>
<td>95</td>
<td>7</td>
<td>7%</td>
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<tr>
<td>2004</td>
<td>130</td>
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<td>2005</td>
<td>122</td>
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<td>6%</td>
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<td>2006</td>
<td>141</td>
<td>15</td>
<td>11%</td>
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<tr>
<td>2007</td>
<td>120</td>
<td>13</td>
<td>11%</td>
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<tr>
<td>2008</td>
<td>164</td>
<td>26</td>
<td>16%</td>
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<tr>
<td>2009</td>
<td>139</td>
<td>15</td>
<td>11%</td>
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</table>

Totals: 1310 | 144 | 11%
Orphan Drug Approvals 1997 to 2009

- 195 products with orphan designation received FDA approval from 1997 to 2009*
- 30 approvals address ultra rare diseases
  - This equates to ≈15% over study timeframe
- There is no significant trend in the number of orphan approvals (average of 15/year)
- Number of ultra rare approvals per year is small (average 2.3/year), with a slight upward trend over study timeframe

<table>
<thead>
<tr>
<th>Year</th>
<th>All Orphan Approvals</th>
<th>Ultra Rare Approvals</th>
<th>Ultra Rare %</th>
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<tr>
<td>1997</td>
<td>18</td>
<td>2</td>
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<td>1998</td>
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<td>2006</td>
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<td>2009</td>
<td>13</td>
<td>4</td>
<td>31%</td>
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<tr>
<td>Totals</td>
<td>195</td>
<td>30</td>
<td>15%</td>
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* As of November 15, 2009
Approvals rate flat relative to designations
Both for drugs treating all Orphan and ultra-rare diseases

All Orphan Designations and Approvals

Ultra-Rare Designations and Approvals

# of Designations and Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Orphan Designations</th>
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<td>2009</td>
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At the current rate of approval, it will take 150 years to treat 50% of ultra rare disorders in the database.
The development block can also occur before Orphan designation ever happens

- “Stalled Drug Development Projects at the Preclinical Stage”
  - Kakkis EverLife Foundation study underway by Brigitte Miyamoto
  - PubMed/MD’s searched for successfully treated animal models
  - Must be either recombinant protein or small molecule therapeutic
  - Absence of specific treatment other than a palliative one was confirmed through Google and PubMed searches
  - Presence or absence of clinical trials ascertained through Clinicaltrials.gov
- Approximately 25 diseases identified to date
- All diseases with successful likely translatable treatments
- Common problems:
  - Ultra-rare
  - Difficult disease biology that does not fit current drug development paradigms: e.g. narrow developmental stage or long time course
Mucopolysaccharidosis VII

Ultra-rare lysosomal storage disease caused by deficiency of β-glucuronidase

- Liver enlargement, skeletal deformations, developmental delay
- MPS VII is ultra rare: 1:~1,000,000+
  - Sly knows of 40 living patients
- Enzyme therapy successful 16 years ago
- Three approved MPS Enzyme Therapies
- Program unable to obtain clinical development investment with reasonable study design

X-Linked Hypohidrotic Ectodermal Dysplasia

Ectodysplasin A (EDA) deficiency

- Absence or deficient function of teeth, hair, and sweat glands; life-threatening high fever is a risk
- Rec. EDA injected only at birth restores normal phenotype in mouse and dog models
- Only effective at birth but “curative”
- Results reported in 2003
- Clinical development is difficult
  - No markers and no regulatory precedent
  - No newborn screening

Roadblocks in the translation of science into medicine: More challenges for rare diseases than common diseases

• Diseases are too rare or have “inconvenient biology”
  • Lack of knowledge about the disease and its course to design studies

• Lack of a defined regulatory path
  • New endpoints and lack of surrogates or biomarkers
  • Creates uncertainty and holds up investment

• Expectations for development requirements are too great for many rare diseases
  • Cannot expect to spend ~$100 million for diseases with 200 patients

• Too large a risk and cost to invest in the smaller markets
  • Better investment are new acne creams or 100th+ form of morphine
Aldurazyme® (laronidase)  
A story of success and yet tragedy

First clinical study ever to treat MPS I

- Open-label study in 10 patients
- Surrogate measures of Storage
  - Reduction in Liver/spleen size & urine GAG
- Strong positive data in canine MPS I
- Similar to Ceredase® for Gaucher

REPLACEMENT THERAPY FOR INHERITED ENZYME DEFICIENCY — MACROPHAGE-TARGETED GLUCOCEREBROSIDASE FOR GAUCHER'S DISEASE

Norman W. Barton, M.D., Ph.D., Roscoe O. Brady, M.D., James M. Damsokia, Ph.D., Adrian M. Di Boscoglio, M.D., Samuel H. Doppelt, M.D., Suvigol C. Hill, M.D., Henry J. Mankin, M.D., Gary J. Murray, Ph.D., Robert J. Parker, M.D., Charles E. Argooff, M.D., Raji P. Grewal, M.D., Kian-Ti Yu, M.D., and Collaborators*
First study with strong positive results based biochemical and storage measures of disease

- **Liver Size**
- **Urine GAG**
- **Shoulder Restriction**

P<0.001  P<0.001  P<0.001

**FDA rejected the surrogate primary endpoints because there was no independent validating human data**

The New England Journal of Medicine

**ENZYME-REPLACEMENT THERAPY IN MUCOPOLYSACCHARIDOSIS I**

Emil D. Kakkis, M.D., Ph.D., Joseph Musunseri, M.D., Ph.D., George E. Tuller, M.D., Ph.D., Lynn Warner, M.D., Ph.D., John Belmonte, M.D., Ph.D., Merry Passage, M.S., Barbara Benowski, R.N., Jeffrey Phillips, M.D., Robin Donaisow, M.D., Irwin Waldt, M.D., Richard Hoft, M.D., and Elizabeth F. Neufeld, Ph.D.
Aldurazyme eventually approved after a 3 year delay

- Delayed again after Phase 3 related to statistics
  - The most powerful appropriate statistics method was not allowed by FDA
- BioMarin nearly failed more than once
- Advisory Committee disagreed with FDA
  - Voted drug effective 12-0 on 1/13/2003

3 year delay
Costs driven dramatically higher due to the delay

- Challenges with choice of surrogate/biomarker measures
- Use of less powerful statistics by FDA request
- Lack of experience and knowledge at FDA
  - Ultra rare disease
  - Only about 200 on treatment in US

Program
- Start 4/97
- Start study 12/97
- Study End 10/98
- Pre-BLA 11/99
- Start Phase 3 12/2000
- Pre-BLA 12/2001
- File BLA 5/2002
- Approval April 2003

Surrogates Rejected

Extension Data Required by FDA

AdCom 1/15/03

3 year delay

Investment
- ~$30 million

Investment
- $>100 million
Major Development Issues for Rare Diseases

- **#1 Accelerated approval regulations are nearly impossible to use**
  - Rarely enough clinical data to support use of surrogates or biomarker endpoints like those used in Cancer and AIDS

- **#2 Standard study designs/analyses are insensitive**
  - Rare diseases are too heterogeneous and complex
  - Difficult to succeed in small studies even if drug works

- **#3 Insufficient expertise and resources exist at FDA**
  - Limited knowledge about biochemical/genetic disorders
  - Not enough resources and specially trained staff to support review
What should it take for an ultra-rare disease to use the Accelerated Approval Pathway?

- **Level 3 surrogate:** “reasonably likely to predict benefit” per Subpart H regulations*
  - The meaning is not defined and this is the problem

- **Fleming’s requirements for a surrogate**
  - Must accurately represents a direct effect on a clinical outcome, not a parallel pathway to disease mechanism
  - Clinical evidence that intervention is not adverse
  - Must fully capture net effect on clinical endpoint
  - Must be strong and durable effect
  - Specific to a drug MOA and specific indication

* Fleming 2005 “Surrogate Endpoints and FDA’s Accelerated Approval Process”, p72
Accelerated Approval Process
Developed in the face of the AIDS Crisis

- AIDS activists swarmed FDA in late 80’s/early 90’s
- 1992: FDA creates “Accelerated Approval”
  - New Regs allow use of a surrogate (CD4) endpoint for approval if “reasonably likely to predict clinical benefit”

- What happened?

  Largest surge ever in drug innovation
  - 25 drugs approved in 16 year period after reg. change
  - Six different mechanisms of actions
  - All approved under Subpart H accelerated approval
  - Most successful change since the Orphan Drug act
Real Drug Innovation
25 new drugs and 4 combinations approved in a 16 year period

New Accelerated Approval Regulations put into Effect
29 drugs in a 16 year period All accelerated approvals
Yet few diseases categories benefit from Accelerated Approval Regulations: Cancer and AIDS

Usage of the Subpart H or E approvals: 64 NDA’s and 9 BLA’s since 1992

*Only 1 genetic disease treatment approved via Accel. Approv. in 16 years

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Number of Accelerated Approvals</th>
<th>Surrogate endpoint</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>25</td>
<td>Tumor load/PFS</td>
<td>Most pivotal studies without a control group</td>
</tr>
<tr>
<td>HIV</td>
<td>29</td>
<td>CD4 or viral load</td>
<td>Combination therapies also approved</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>Variety</td>
<td>PAH, MS, hormones, iron, Crohns, antibiotics</td>
</tr>
<tr>
<td>Genetic</td>
<td>1</td>
<td>Renal pathology</td>
<td>Fabrazyme</td>
</tr>
</tbody>
</table>

Taken from the FDA.gov website table on accelerated approvals

Proposed qualification criteria for surrogate endpoints in studies of ultra-rare diseases

- Disease basis and mechanism well understood
- Drug mechanism of action is direct at cause and understood
  - Directly in line of disease process mechanism
- **Surrogate marker has direct relationship to disease**
  - Sensitive and specific assay with large dynamic range
  - Sampling compartment relevant to disease compartment
- **Preclinical/Clinical qualification**
  - Preclinical studies show dynamic dose-response on pathology
  - Clinical effect optional in an adequate animal model
  - Clinical severity or progression proportional to marker concentration in cross-sectional study
Analyzing clinical data in heterogeneous and rare patients

- Patient selection possible for only one endpoint
  - Cannot select and cannot hit other endpoints
  - Intent to treat (ITT) analysis obscures many effects
- Statistics for two group comparisons insensitive
  - Heterogeneity at baseline creates large “noise” factor
- Current designs miss multiple effects of a drug
  - Composite endpoints not feasible without “validation”
RECOMMENDATION 6: More research on alternative designs is needed. Appropriate federal agencies should increase support for expanded theoretical and empirical research on the performances of alternative study designs and analysis methods that can be applied to small studies. Areas worthy of more study may include theory development, simulated and actual testing including comparison of existing and newly developed or modified alternative designs and methods of analysis, simulation models, study of limitations of trials with different sample sizes, and modification of a trial during its conduct.
Plan for studying clinical study design and analyses

- Scientific Advisory Committee (SAC) formed
  - Janet Wittes, Tony Lachenbruch, LJ Wei, Brent Blumenstein, Larry Friedmann (likely)
- Have data from 5 ultra-rare disease products committed to SAC by biotech companies
- Will evaluate and model with existing data to establish more powerful analyses and designs
- Workshops and draft guidance proposals
- Work with FDA to draft new guidances
  - Design and statistics of clinical studies for rare diseases
#3 Personnel training and experience

Additional experienced staff are needed at FDA for rare disorders

_Created a new Office of Drug Evaluation for Biochemical and Genetic Disorders_

- Consolidate new staff with existing expertise
- Add qualified specialists for all review disciplines
- Develop and establish guidelines for rare diseases
- Improved connection to the Orphan Product Office
- Improved academic environment/links with NIH
Summary of Proposed Solutions
For Accelerating Rare Disease New Drug Development

• New ODE with additional staff with time/experience
• New guidance on small clinical studies/analyses
• New guidance for qualifying surrogates in ultra-rare

• Patent extensions for new orphan indications added to label of patent protected drugs
  – 2-3 month patent extensions for each rare indication added to the label with a limit of 3-5 new indications
  – High quality clinical studies required for supplemental filing
  – Potentially dozens of diseases might get a relatively low cost treatment priced for the large main market
Acknowledgements

• Kakkis EveryLife Foundation (KELF) staff
  – Brigitte Miyamoto, John Ditton, Julia Jenkins, Annie Takeuchi

• BioMedical Insights: Chris Nicita, Andrew Kloek

• BioMarin, Genzyme and Shire for providing clinical data

• KELF Science Advisory Board

• KELF Regulatory Advisory Board

• Patient groups for their endorsements

• Institute of Medicine for this invitation