ACCELERATING BIOTECHNOLOGY INNOVATION FOR RARE DISEASES:
Challenges and solutions

Emil D. Kakkis, M.D., Ph.D.
President and Founder, EFRD
Also CEO, Ultragenyx Pharmaceutical Inc.

April 17, 2013

No Disease Is Too Rare to Deserve Treatment
EveryLife Foundation:

- Dedicated to Accelerating Biotechnology Innovation for Rare Disease Treatments
- Advocate for practical and scientifically sound change in policy and law to increase the efficiency & predictability development process
- We believe:
  - No disease is too rare to deserve treatment
  - All treatments should be safe & effective
  - We could be doing more with the science we already have
Launched May 2009 at the Rare Disease Summit, Washington DC

1) Improving specialization of drug reviews
2) Improved access to biomarker-based approvals
3) Greater acceptance of alternative clinical trial designs
181+ CureTheProcess Campaign Partners
The development process

Great Science

And then a miracle happens

No Disease Is Too Rare to Deserve Treatment
IRDiRC Goal: 200 new treatments by 2020
Can we achieve this?

Lost in Space  Wandering in Wilderness  Valley of Death  Clin-Reg Hell  Reimbursement Purgatory

IDEA  Model POC  Tox., IND/CTA Ph. 1 Study  Ph2/PH3 NDA  Reimbursement

0  Yr 5  Yr 10  Yr 13  Yr 15
Cost/demands for rare disease drug development are rising

- Requirements are rising each year
  - More tox, larger studies, more PMC’s
- Costs for many programs in rare disease exceed $100M investment and some $300M or more
- 200 treatments times $200M is $40 Billion if development is perfect with no misses
  - Dollars or euros does not matter
Transforming science into medicine:
Key challenges for rare diseases

- Current paradigm for clinical development is neither optimal nor efficient
- Biomarkers as surrogate endpoints are rarely available or acceptable
- Safety testing needs rationalization as costs rise
- Incentives are not sufficient for many very rare diseases, especially for repurposing drugs
Paradigm for pivotal clinical studies

1) Start with a RD, a treatment with one dose
2) Choose a single primary endpoint regulators understand but often not used for that RD
3) Select patients that have abnormalities in that particular endpoint for study
4) Design a simple two arm study with one dose level that is not optimized to each patient
5) Hope to get a positive result in the one endpoint
6) Explain to doctors and reimbursers why you have data only on the one primary endpoint
Problems for the current paradigm
Not efficient for heterogeneous rare diseases

- Narrow our evaluation to fit the statistical plan
- Treat only patients that have the problem as treating others would dilute result
- Get data on one dimension of disease and safety on one segment of the population
- Get critiqued later for the value of changing the one endpoint, without other endpoints

*Is this really right? One dimension of one disease in some patients to meet a simplistic stat plan?*
Statistical considerations force drug development into unscientific decisions

- Religious adherence to simplistic hypothesis testing model
  - Single test, single endpoint,
- Misuse of Intent to Treat analyses
  - Confounding study of heterogeneous diseases
  - Forced to select on one endpoint, lose on others
- Single endpoints/domains not efficient or accurate estimate of disease
  - Missing full understanding of treatment effect
Better paradigm for clinical development in small populations of heterogeneous subjects

- Treat all patients in the controlled study
  - Compare each patient with themselves
- Evaluate across 5 or 6 important endpoints
- Stratify/subset analyses prospectively for abnormality at baseline, age, severity, stage, etc
- Titrate the drug to individual maximum effect
- Test efficacy across many important domains
  - Combine power of treatment effect across domains using novel approaches to statistics
- Gain safety information on a broader population
Blind start clinical study design

- All patients receive treatment at some point
- Patients are blind to the cross from placebo to drug
- Patients are compared to themselves, not placebo

1) Power is increased based on modeling
2) Richer dataset with placebo and treatment data
Challenges with Endpoints:
Laronidase for MPS I
Phase 3 Study Positive? Yes and No

**FVC** (Patients selected for <80%)  
**6MWT** (No patient selection)

*Also missed on sleep apnea, range of motion and visual acuity as individual ITT analyses: only subsets would hit*
Multi-Domain Analysis Example
Laronidase for MPS I Phase 3 *

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Aldurazyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>FVC</td>
</tr>
<tr>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>20</td>
<td>43</td>
</tr>
<tr>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Clinically Significant Changes
- Improve
- No Change
- Decline
- Not Available

* Courtesy of G. Cox, Genzyme
Phase 3 Study: Multi-domain responders
More powerful than single endpoint analyses

Responders
59% Aldurazyme
22% Placebo
(p=0.016)

Mean Net Change
1.0 Aldurazyme
-0.4 Placebo
(p=0.003)
Biomarker-based approvals (accelerated approval) are too difficult

- Biomarkers lack historical information
- Insufficient clinical outcome information
- Nearly impossible to gain acceptance
- Often reasonable if not excellent science
- Need a predictable way to qualify biomarkers for high unmet medical need situations
First 16 Years of BioMarker Endpoints Utilization of Accelerated Approval Pathway for Cancer, HIV and Genetic Indications
Usage of the Subpart H or E approvals: 64 NDA’s and 9 BLA’s since 1992*

<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>26</td>
<td>Variety</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>17</td>
<td>Variety</td>
<td>PAH, hormones, iron, Crohns, MS, 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
Analysis of impact from better access to Accelerated Approval

BioMarker endpoints could yield 3x more diseases treated for the same investment

- 36 drugs developed for same 1 billion USD using biomarker primary endpoints

Article at http://www.ojrd.com/content/6/1/49
Success in Moving Legislation Through US Congress: ULTRA/FAST
New law expands access to Accelerated Approval process

- Drafted legislation with Reps. Stearns & Towns –ULTRA/FAST Acts
- Vigilant communication and cooperation with key stakeholders
- FAST language inside the PDUFA V bill (FDASIA, S. 3187)
- Organized the patient community as a political force

*FDASIA signed by President Obama July 9, 2012*
ULTRA/Fast –
Next Steps for Implementation: White Paper to Guide the Guidance

- Sec. 901. Enhancement of accelerated patient access to new medical treatments. (ULTRA/FAST)
  - Considerations. – In developing the guidance . . . . the Secretary shall consider . .
  - (2) how to incorporate *novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical*.

- Draft guidance is due from the FDA in July
- Working group to draft a Whitepaper for the Guidance
- *Reviewed at Foundation’s next workshop on Wednesday, May 15, 2013 in Washington, DC.*
Ultragenyx Developing Products for 11 different genetic diseases currently

Metabolic genetic diseases

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical</th>
<th>Pre-IND</th>
<th>IND</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>UX001 Sialic Acid (Extended Release)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hereditary Inclusion Body Myopathy</td>
<td></td>
</tr>
<tr>
<td>UX007 Triheptanoin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 Fatty Acid Oxidation Disorders + 2 others</td>
<td></td>
</tr>
<tr>
<td>UX003 rhGUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>β-glucuronidase (rhGUS) for MPS 7 Sly Syndrome</td>
<td></td>
</tr>
<tr>
<td>UX004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Undisclosed Enzyme Replacement Therapy</td>
<td></td>
</tr>
</tbody>
</table>
Treating Rare Diseases solutions

• We can do better than we are
  – High costs, long time and expensive drugs
• Improve the clinical trial paradigm
• Allow more qualified biomarker endpoints
• Rationalize safety testing requirements
• Plus a few more things.....
Questions?

Be Sure to Follow us

- [http://www.facebook.com/EveryLife4RareDiseases](http://www.facebook.com/EveryLife4RareDiseases)
- [http://twitter.com/#!/curetheprocess](http://twitter.com/#!/curetheprocess)