REGULATORY WORKING GROUP WEBINAR: NAVIGATING THE FDA ACCELERATED APPROVAL PROCESS: RARE DISEASE CASE STUDIES
M. Bronstein
Senior Director, Advocacy & Science Policy

Co-Chair: Stephen Smith, Steve Smith
Plains & National MPS Society

Co-Chair: Lynne Fahey McGrath, VP, Regulatory Affairs, RegenXBio Inc.

No Disease Is Too Rare to Deserve Treatment
Agenda

→ Welcome and Community Congress Background
  - Max Bronstein, Senior Director, Advocacy & Science Policy, EveryLife Foundation for Rare Diseases
  - Community Congress Regulatory Co-Chairs: Lynne McGrath, RegenXBio & Steve Smith, National MPS Society

→ Overview of Accelerated Approval Pathways for Rare Disease Therapies
  - Jonathan Goldsmith, Associate Director for Rare Diseases, Food & Drug Administration (FDA)

→ Industry & Patient Organization Case Studies: the Accelerated Approval Pathway
  - Lynne McGrath, Vice President of Regulatory Affairs, RegenXBio
  - Shamim Ruff, Senior Vice President, Regulatory Affairs & Quality, Sarepta
  - Isabelle Lousada, President & CEO, Amyloidosis Research Consortium

No Disease Is Too Rare to Deserve Treatment
Mission and Core Principles

Accelerating biotech innovation through science-driven public policy

What We Believe:
- No disease is too rare to deserve treatment
- Rare disease therapies should be safe and effective
- We could do more with the science we already have

What We Do:
- Advocate for evidence-based public policy and regulatory reform

How We Get it Done:
- Grassroots action
- Scientific and policy expertise
Public Policy Objectives

The Foundation seeks practical policy solutions that will:

- Close the innovation gap for the 95% of rare diseases that have no FDA-approved treatment
- Ensure patients receive earliest access to diagnostic and treatment opportunities
- Improve the regulatory process and advance regulatory science for rare disease therapies
- Enhance the patient voice in policymaking, drug development and regulatory decision-making
Accessing the accelerated approval pathway for rare disease therapeutics

The accelerated approval pathway was originally promulgated in 1992 by the US Food and Drug Administration (FDA) to help speed access to therapeutics for serious and life-threatening diseases. For diseases like AIDS, data from biomarkers like blood T-cell counts were considered reasonably likely to predict the longer-term clinical benefit of drugs against HIV. These regulations have been instrumental in the development of many HIV drugs, multidrug cocktails (highly active anti-retroviral therapy, or HAART) and numerous cancer drugs.

During the first 16 years of the accelerated approval pathway, a total of 73 new chemical entities (NCEs) were approved by the FDA (64 new drug applications (NDAs) and 9 biologic license applications (BLAs)). Among these approvals, 29 drugs (including four combinations) were approved for HIV and 26 new NCEs were approved for cancer, along with 17 therapies for infections, multiple sclerosis, pulmonary arterial hypertension and other indications. For treating cancer and HIV, accelerated approval has been an enormous success in driving drug innovation, and the FDA and the drug sponsors and companies should be applauded for their efforts in allowing this innovation to move forward and change people’s lives.

That said, in the same 16-year period, only one rare genetic disease therapy, Fabrazyme (agalsidase beta), was approved. The evidence supporting accelerated approval for Fabrazyme was based on a biomarker, the resolution of lysosomal storage pathology on renal biopsies. Despite the fact that many rare genetic diseases have relatively distinct biochemical markers directly in the genetic pathway of disease, makers of drugs for rare genetic diseases are not accessing the accelerated approval pathway using novel biomarkers.

In this article, we argue that clearer, more practical qualification criteria are needed to foster the development of therapies for rare genetic diseases. Our arguments are based on a white paper produced by a working group of foundation, industry and academic representatives assembled by the EveryLife Foundation for Rare Diseases (Novato, CA, USA) in 2014.

A poorly defined biomarker qualification process for rare diseases

The qualification process for novel biomarker endpoints as likely predictive of clinical benefit has been too difficult in rare genetic diseases, leading to some treatments for ultra-rare or challenging diseases not being successfully developed or studied. Although FDA issued new guidance for expedited programs, including accelerated approval and the Qualification Process for Drug Development Tools, the qualification process for novel biomarkers as primary endpoints in the accelerated approval pathway remains insufficiently defined. Progress is needed in establishing a more predictable pathway, including a set of reasonable scientific criteria to provide greater access to accelerated approval for rare genetic disease treatments with novel biomarker endpoints.

Flexibility by the FDA has been an important part of the approval pathway in rare diseases and is critical for approval of needed therapies. However, flexibility alone is not enough—we need clear and practical qualification criteria to foster the development of therapies for untreatable ultra-rare and difficult-to-treat genetic diseases.

In response to criticism regarding accelerated approval accessibility for rare diseases, some experts have noted that rare disease treatments have been approved at times through the standard approval pathway using biomarker endpoints. To evaluate whether any novel biomarkers have been used in any orphan drug approvals recently, whether by accelerated approval or not, we analyzed all FDA orphan drug approvals from 2009 to 2014 (refs. 1,2 and Supplementary Table 1). Of the 91 new molecular entities approved as orphan drugs in that period, none included a novel biomarker primary endpoint. Figure 1 shows...
Patients as key partners in rare disease drug development

Max Bronstein and Emil D. Kakkes

Rare disease drug development could benefit substantially from increased patient input to enhance understanding of the key aspects of disease impact and patients’ perspectives on the benefit-risk profile of potential therapies.

We are currently witnessing a shift in the culture of drug development, whereby drug sponsors and regulatory agencies are showing increased interest and awareness in incorporating the perspectives of patients. In the rare disease field in particular, the lack of quantitative understanding of disease burden and progression using primary interictal patient experience measures is a significant limitation. The study should guide the clinician in developing treatment options by helping construct potential patient- and family-reported outcomes.

A comprehensive understanding of disease burden will help guide the development of patient-reported outcome measures. Patient engagement in drug development can lead to the creation of more effective therapies and less burdensome treatments.

Figure S1 | Patient engagement during the drug development process. IND, investigational new drug.
Newborn Screening SB 1095

- Authored California legislation to enhance and expand newborn screening
- Requires screening of MPS I & Pompe disease
- Creates a higher standard for screening based on recommendations from public health experts
- Governor Jerry Brown signed SB 1095 on Friday, September 16, 2016!
21st Century Cures & OPEN ACT

ACCELERATE THE PACE OF CURES

No Disease Is Too Rare
- Foster **collaboration** between patient organizations and industry
- Serving as strategic **advisory committees**
- On call to respond to **urgent policy issues** and opportunities
Newborn Screening Co-Chairs: Toolkit Development

EveryLife Foundation – Staff Support

Public Policy Co-Chairs: Ted Buckley, Shire Christina Might, NGLY1.org
Expanded Access – Scientific Workshop

Regulatory Science Co-Chairs: Lynne McGrath, RegenxBio
Steve Smith, National MPS Society
Regulatory Science Webinar Series
DATE: Friday, October 16, 2015

TO: The U.S. Food and Drug Administration


FROM: Regulatory Science Working Group, Community Congress Program, EveryLife Foundation for Rare Diseases

Working Group Membership:
- Pat Furlong, President, Parent Project Muscular Dystrophy
- Annie Kennedy, Senior Vice President – Legislation & Public Policy, Parent Project Muscular Dystrophy
- Frank Rivera, President, Sarcoidosis of Long Island
- Lisa Schill, Vice President, RASopathies Network USA
- Jack Kelly, President, Lymphangiomatosis & Gordham’s Disease Alliance
- Steve Smith, Chief Patient Advocate, Medidata Solutions, & MPS Parent Advocate
- Mladen Bozik, Head of Global Regulatory Policy & Intelligence, Shire Pharmaceuticals
- Melissa Hogan, President, Saving Case & Friends Inc.
- Annie Achee, Board Member, National Leiomyosarcoma Foundation
- May Orfali, Global Medical Lead – Rare Disease Unit, Pfizer Inc.
- Lynne McGrath, Vice President – Regulatory Affairs, RegenxBio
- Bill McCue, President, PRP Alliance Inc.
- Badri Rengarajan, Board Member, Pemphigus & Pemphigoid Foundation
- Laura Mitic, Director of Translational Research, The Bluefield Project to Cure Frontotemporal Dementia
- Max Bronstein, Senior Director - Advocacy & Science Policy, EveryLife Foundation for Rare Diseases
- Emil Kakkis, MD, PhD, President & Founder, EveryLife Foundation for Rare Diseases

No Disease Is Too Rare to Deserve Treatment
FREE November Meeting

Annual Meeting: Wednesday, November 16, 2016
The American Association for the Advancement of Science (AAAS)
1200 New York Avenue, NW Washington, DC

(Pictured: Dr. Phil Reilly, Venture Partner, Third Rock Ventures; Dr. Emil Kakkis, President, EveryLife Foundation for Rare Diseases; Cheryl Jaeger, Principal, William & Jensen; Emily Shetty, Consultant, The Stanton Park Group; Dr. Richard Pan, California State Senator)

No Disease Is Too Rare to Deserve Treatment
Membership

- Over 60 patient groups and 15 industry members
- FREE for Patient Groups to Join
- Thank you members and co-chairs!
Thank You!

- To learn more about Community Congress and to join: [www.everylifefoundation.org](http://www.everylifefoundation.org)
- Email: mbronstein@everylifefoundation.org
Overview of Accelerated Approval Pathways for Rare Disease Therapies

Jonathan C. Goldsmith, M.D.
Associate Director Rare Diseases Program
Office of New Drugs
Center for Drug Evaluation and Research/FDA
EveryLife foundation Community Congress Regulatory Webinar
October 25, 2016
Disclosures

• No Conflicts of Interest
• Nothing to Report
• Opinions expressed are personal and do not reflect those of the FDA
Expediting Rare Diseases Drug Development

- Programs have been developed to target serious diseases with unmet medical needs when a new treatment could provide meaningful clinical benefit.
Expediting Rare Diseases
Drug Development

• Fast Track
  – FDAMA 1997/FDASIA 2012

• Breakthrough Designation
  – FD&C Act/FDASIA 2012

• Priority Review
  – PDUFA 1992

• Accelerated Approval

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
There are TWO approval pathways in the US

**traditional** (regular or “full”) approval and

**accelerated approval**

the statutory standards are the same for both
demonstration of substantial evidence based on adequate and well-controlled clinical study(ies)
Approval Pathways

• **Both** pathways must meet the statutory standards:
  • Substantial evidence based on adequate and well-controlled clinical study(ies)

• Accelerated approval expedites new drug availability for *serious unmet need* by relying on a more readily measured **surrogate** or **intermediate clinical endpoint**
Approval Pathways

- Consider accelerated approval when a lengthy trial would be needed to measure intended clinical benefit of a drug for a serious unmet need
Approval Pathway: The Importance of the Endpoint

• Accelerated Approval Pathway depends on strength of evidence about ability of the endpoint to predict an effect on irreversible morbidity or mortality (clinical benefit)

• A surrogate or intermediate clinical endpoint is a marker thought to predict clinical benefit, not itself a measure of benefit: lab value, radiographic image, physical sign, etc.
Accelerated approval: a pathway to speed regulatory approval

- Candidate drug must provide a meaningful advantage over available therapies to treat a **serious** condition, generally irreversible morbidity or mortality

- Relies on a **more readily measured surrogate** (or intermediate clinical) **endpoint**

- A post-approval confirmatory study evaluating a **direct clinical endpoint** is generally required

 Expedited Programs for Serious Conditions guidance, and 21CFR 314 Subpart H/biologics 21CFR Part 601, Subpart E
Clinical vs. surrogate endpoints

• **Direct clinical** endpoint: characteristic or variable that *directly* measures a therapeutic effect - how a patient feels, functions, or survives

• **Surrogate** endpoint for accelerated approval: marker *thought to predict* clinical benefit; not itself a measure of benefit
A note about historical controls

• Historically controlled studies can be adequate and well controlled studies in appropriate cases

   HOWEVER

   Such studies have many interpretability issues

   THEREFORE

• Placebo or active controlled trials remain the goal for rare (and common) diseases whenever ethically and practicably feasible
US approval essentials

- Substantial evidence of effectiveness for treatment of the proposed indication
- Demonstration that the benefits of the drug outweigh its risks for the patient population for which the drug is indicated (21CFR 314.50)
US approval essentials

 ✓ Manufacturing that ensures product identity, strength, quality (purity)

 ✓ Evidence-based drug labeling that adequately guides providers and patients to use the drug safely and effectively
Contact Us

CDER Office of New Drugs
Rare Diseases Program

301-796-4061

Jonathan Goldsmith MD, Associate Director

- Larry Bauer, Regulatory Scientist
- Althea Cuff, Science Policy Analyst
- Lucas Kempf, Medical Officer
- Kathryn O’Connell, Medical Officer

CDERONDRareDiseaseProgram@fda.hhs.gov
Accelerated Approvals in Rare Diseases

Lynne Fahey McGrath, MPH PhD
Vice-President Regulatory Affairs
REGENXBIO Inc
October 25 2016
Acceleration Opportunities at FDA
For rare diseases

- **Myalept** – rare metabolic disease
  - Fast Track
  - Priority review with delay
  - Full approval – not accelerated

- **Carboglu** – ultra rare metabolic disease
  - No fast track
  - Priority Review
  - Full Approval

- **Zykadia** – rare cancer
  - Breakthrough therapy
  - Priority review
  - Accelerated Approval
Myalept: Rare Metabolic Disease

- Indication: MYALEPT is a leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

- Fast track designation granted 2001

- Rolling submission
  - Initial documents submitted April 2, 2012
  - Final document submitted March 27, 2013
  - PDUFA date November 27, 2013
  - Major amendment submitted June 24, 2013
  - FDA Approval date, February 24, 2014

- Full approval: Data supports clinical benefit

- Limited indication

- Significant post approval safety monitoring
# Myalept: Rare Metabolic Disease
Limited data for approval

Table 3: Results in an Open-Label, Single-Arm Study in Patients with Generalized Lipodystrophy Treated with MYALEPT (N=48)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Baseline</th>
<th>Change from Baseline at Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>35</td>
<td>8.5 (2)</td>
<td>-2 (1.5)</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>37</td>
<td>174 (85)</td>
<td>-49 (75)</td>
</tr>
<tr>
<td>Fasting Triglycerides (mg/dL)</td>
<td>36</td>
<td>348 (176, 769)</td>
<td>-184 (-643, -21)</td>
</tr>
</tbody>
</table>

SD = standard deviation; Q = quartile

Single arm trial does not allow p-values to be reported

Compelling results allows single trial for registration

Low patient numbers
Carbaglu
Ultra rare metabolic disease

Indication: Adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) and Maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS

- October 1998: Orphan Designation
- July 11, 2008: NDA submitted, subsequently withdrawn due to deficiencies
- June 17, 2009: NDA submitted and “filed”
- Priority Review granted: 6 month review clock
- March 17, 2010: Full approval granted
Carbaglu
Ultra rare metabolic disease

Table 3: Plasma ammonia levels at baseline and after treatment with Carbaglu

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Statistics (N = 13*)</th>
<th>Ammonia** (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>N</strong></td>
<td>13</td>
</tr>
<tr>
<td>(prior to first treatment with Carbaglu)</td>
<td><strong>Mean (SD)</strong></td>
<td>271 (359)</td>
</tr>
<tr>
<td></td>
<td><strong>Median</strong></td>
<td>157</td>
</tr>
<tr>
<td></td>
<td><strong>Range</strong></td>
<td>72-1428</td>
</tr>
<tr>
<td></td>
<td><strong>Missing Data</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td><strong>N</strong></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td><strong>Mean (SD)</strong></td>
<td>181 (358)</td>
</tr>
<tr>
<td></td>
<td><strong>Median</strong></td>
<td>65</td>
</tr>
<tr>
<td></td>
<td><strong>Range</strong></td>
<td>25-1190</td>
</tr>
<tr>
<td></td>
<td><strong>Missing Data</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td><strong>N</strong></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td><strong>Mean (SD)</strong></td>
<td>69 (78)</td>
</tr>
<tr>
<td></td>
<td><strong>Median</strong></td>
<td>44</td>
</tr>
<tr>
<td></td>
<td><strong>Range</strong></td>
<td>11-255</td>
</tr>
<tr>
<td></td>
<td><strong>Missing Data</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td><strong>N</strong></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td><strong>Mean (SD)</strong></td>
<td>27 (11)</td>
</tr>
<tr>
<td></td>
<td><strong>Median</strong></td>
<td>25</td>
</tr>
<tr>
<td></td>
<td><strong>Range</strong></td>
<td>12-42</td>
</tr>
<tr>
<td></td>
<td><strong>Missing Data</strong></td>
<td>8</td>
</tr>
<tr>
<td><strong>Long-term</strong></td>
<td><strong>N</strong></td>
<td>13</td>
</tr>
<tr>
<td>Mean: 8 years</td>
<td><strong>Mean (SD)</strong></td>
<td>23 (7)</td>
</tr>
<tr>
<td>Median: 6 years</td>
<td><strong>Median</strong></td>
<td>24</td>
</tr>
<tr>
<td>1 to 16 years</td>
<td><strong>Range</strong></td>
<td>9-34</td>
</tr>
<tr>
<td>(last available value on Carbaglu treatment)</td>
<td><strong>Missing Data</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

Very low numbers of patients

Dramatic decrease in ammonia levels
Zykadia (Crizotinib) Rare Cancer

- Indication: treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to Crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established.

- IND filed 2010
- March 6, 2013: Breakthrough Therapy Designation was granted
- March –December 2013: 8 meetings held
- September 27, 2013: Zykadia was designated as an orphan drug
- December 24, 2013: rolling submission completed
- August 24, 2014: PDUFA date priority review
- April 29, 2014: Accelerated approval granted (4 months)
  - Post approval commitment to demonstrate clinical benefit
# Zykadia (Crizotinib)
## Rare Cancer

Table 4: Overall Response Rate and Duration of Response\(^1\) in Patients with ALK-Positive NSCLC who Receive Prior Crizotinib in Study 1

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Investigator Assessment (N=163)</th>
<th>BIRC Assessment (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate (95% CI)</td>
<td>54.6% (47, 62)</td>
<td>43.6% (36, 52)</td>
</tr>
<tr>
<td>CR</td>
<td>1.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>PR</td>
<td>53.4%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Duration of Response, median (months) (95% CI)</td>
<td>7.4 (5.4, 10.1)</td>
<td>7.1 (5.6, NE)</td>
</tr>
</tbody>
</table>

\(^1\)Overall Response Rate and Duration of Response determined by RECIST v1.0
BIRC, blinded independent review committee; CR, complete response; NE, not estimable; PR, partial response.
## Recent product approvals with Acceleration

<table>
<thead>
<tr>
<th>Product</th>
<th>MOs</th>
<th>Yr</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCALIVA (P, A)</td>
<td>10.9</td>
<td>2016</td>
<td>FOR THE TREATMENT OF PRIMARY BILIARY CHOLANGITIS (PBC) IN COMBINATION WITH URSODEOXYCHOLIC ACID (UDCA) IN ADULTS WITH AN INADEQUATE RESPONSE TO UDCA, OR AS MONOTHERAPY IN ADULTS UNABLE TO TOLERATE UDCA</td>
</tr>
<tr>
<td>TECENTRIQ</td>
<td>4.2</td>
<td>2016</td>
<td>INDICATED FOR PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA WHO HAVE DISEASE PROGRESSION…</td>
</tr>
<tr>
<td>VENCLEXTA</td>
<td>5.4</td>
<td>2016</td>
<td>FOR THE TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH 17P DELETION, AS DETECTED BY AN FDA APPROVED TEST, WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY</td>
</tr>
<tr>
<td>PROVAYBLUE</td>
<td>6.0</td>
<td>2015</td>
<td>FOR THE TREATMENT OF PEDIATRIC AND ADULT PATIENTS WITH ACQUIRED METHEMOGLOBINEMIA</td>
</tr>
<tr>
<td>ALECENSA</td>
<td>5.2</td>
<td>2015</td>
<td>FOR THE TREATMENT OF PATIENTS WITH ANAPLASTIC LYMPHOMA KINASE (ALK)-POSITIVE METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC), WHO HAVE PROGRESSED ON OR ARE INTOLERANT TO CRIZOTINIB</td>
</tr>
<tr>
<td>DARZALEX</td>
<td>4.3</td>
<td>2015</td>
<td>FOR TREATMENT OF PATIENTS WITH MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST 3 PRIOR LINES OF THERAPY …</td>
</tr>
<tr>
<td>AGRISSO</td>
<td>5.3</td>
<td>2015</td>
<td>FOR THE TREATMENT OF PATIENTS WITH METASTATIC EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) T790M MUTATION-POSITIVE-NON-SMALL-CELL LUNG CANCER (NSCLC),</td>
</tr>
<tr>
<td>PRAXBIND</td>
<td>7.9</td>
<td>2015</td>
<td>INDICATED IN PATIENTS TREATED WITH PRADAXA® WHEN REVERSAL OF THE ANTICOAGULANT EFFECTS OF DABIGATRAN IS NEEDED FOR EMERGENCY SURGERY/URGENT PROCEDURES AND IN LIFE-THREATENING OR UNCONTROLLED BLEEDING</td>
</tr>
</tbody>
</table>
Conclusion

- Multiple FDA guidance available for industry to gain insights into drug development and approval process
- FDA considers the unique characteristics of patients, unmet need, rarity of disease and the challenges in conducting trials
- FDA provides multiple opportunities for industry sponsors for rare diseases with an unmet need discuss and facilitate development
- FDA does not compromise study quality in any approval
Eteplirsen Accelerated Approval

Shamim Ruff
Sr. Vice President
Regulatory Affairs and Quality
Sarepta Therapeutics
25 October, 2016
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Discussion Items

- Regulatory Framework
- Eteplirsen Case Study
- Regulatory Precedent
Regulatory Framework
Evolution of Regulatory Standards

- **“Substantial evidence” of effectiveness** (FD&C Act Sec 505(d), 1962
  
  “evidence consisting of adequate and well-controlled investigations..”
  
  - Generally intended to require **at least two adequate and well-controlled studies**, each convincing on its own, to establish effectiveness

- Orphan Drug Act, 1983, did not change the approval standards for drugs for rare diseases

- Use of **one adequate and well controlled study** (FDAMA § 115(a), 1997; FDA Guidance, May 1998)

- Historical controls in special circumstances (21 CFR 314.126(b)(2)(v))

- No specific minimum number of patients to establish effectiveness and safety (FDA, *Guidance for Industry Rare Diseases: Common Issues in Drug Development*, August 2015)
Accelerated approval (AA)  
FDASIA, Sec. 901, 2012

♦ Broader use of AA beyond HIV/AIDS and oncology to rare diseases, such as DMD
♦ Requires that FDA seek patient input during drug development and review
♦ Allows for acceptable degree of uncertainty regarding anticipated benefit
  • Surrogate or intermediate clinical endpoints
  • Account for “the severity, rarity, or prevalence of the condition . . .”
  • May involve “fewer, smaller, or shorter clinical trials” (FDA, Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014)
Drug X is indicated for \{state indication\}. This indication is approved under accelerated approval based on \{state effect on surrogate endpoint or clinical endpoint that supported the accelerated approval\} [see Clinical Studies (14.X)].

An improvement in \{identify the specific clinical benefit that remains to be established\} \textbf{has not been established}

Continued approval for this indication may be contingent upon \{either ("verification and description of clinical benefit") or ("demonstration of" followed by identification of the particular expected clinical benefit(s) that will be the objective of the postmarketing study)} \textbf{in confirmatory trials}
Eteplirsen Accelerated Approval

Case Study
Indication:

- EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.
- This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see Clinical Studies (14)].
- A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Dosing and Administration:

- 30 mg/kg weekly IV Infusion
DMD Disease Overview

◆ Pediatric, X-linked, recessive neuromuscular disease
  – ~ 1 in 3,500 to 5,000 males

◆ Mutations in DMD gene prevent production of functional dystrophin protein
  – Vital for muscle structure, function and preservation
  – DMD is due to lack of functional dystrophin

◆ Progressive, debilitating and universally fatal
  – Loss of ambulation during adolescence
    • Leads to downstream complications
  – Premature death (mid-late 20s)

◆ No approved therapies in the US until eteplirsen
Eteplirsen induces the production of dystrophin protein by skipping exon 51

- ~80% DMD mutations amenable to treatment by exon skipping
- US prevalence of DMD: ~9,000 to 12,000 boys
- ~13% of DMD patients amenable to exon 51 skipping

Challenges for Eteplirsen Development

- Small company, limited resources with high manufacturing costs
- Subset of an “ultra-rare” heterogeneous patient population
- Treatment effect must be large for a small patient population
  - Smaller effect size may not be detectable in a small study
- Uncertain development pathway
  - Lack of in-depth epidemiological or natural history data
  - Limited precedence for clinical and biomarker endpoints
    - Which endpoint will respond best?
    - How long it will take to see the required difference?
    - How much or how to measure accurately and reproducibly?
Eteplirsen DMD Clinical Program

**Phase Overview 1**
33: Single IM
   N=7
28: Dose Ranging
   N=19

**Phase 2**
201
   N=12
202
   N=12

**Phase 3**
203: Age 4 - 6
   N=40
   Ongoing
204: Advanced
   N=24
   Ongoing
PROMOVI
   N=120
   Ongoing
How Did We Get To An NDA Submission: Small P2 data set and natural history controls?

- More than a dozen meetings with FDA, lead to a pathway for NDA submission

- Early P2 dystrophin data precluded the initiation of a P3 placebo-controlled study
  - Physicians and patients unwilling to participate in placebo-controlled study

- FDA requested:
  - Additional long term data from the single arm 202 eteplirsen study
  - Natural history (NH) data for comparison to eteplirsen clinical data
  - Additional dystrophin data using validated assays developed in consultation with FDA
2 Options For AA Pathway

- FDA provided 2 options for AA pathway:
  - Use of 6MWT as an “intermediate” clinical endpoint, reasonably likely to predict benefit
    - or
  - Use of dystrophin as a surrogate endpoint, reasonably likely to predict benefit

- Safety data from all 7 studies (n=114)
- Agreed to the design of 2 Confirmatory Studies
ETEPLIRSEN NDA
REGULATORY MILESTONES

2015

- Jun: NDA filed
- Aug: Tentative Ad Comm Date #1
- Oct: NDA submitted
- Nov: Mid-Cycle Communication Meeting

2016

- Jan: Tentative Ad Comm Date #2
- Feb: PDUFA data extended
- Apr: Actual Ad Comm
- Sep: NDA approved
- Late Cycle Meeting
Primary Basis For Efficacy: dystrophin as a surrogate endpoint

- Significant increase in dystrophin protein, using validated Western blot methods from 2 studies:
  - 202 P2 (Week 180 biopsy samples)
  - PROMOVI P3 study (Week 48 biopsy samples)

- Supportive data:
  - 2 additional complementary methods demonstrated statistically significant production of de-novo dystrophin
    - Immunohistochemistry demonstrated correct localization of dystrophin
  - RT-PCR demonstrated exon skipping in all patients tested (3 studies)
  - Sequencing confirmed correct exon skipping
Accelerated Approval Based On The Totality Of Evidence

Clinical Data Provided:

- Comparative Eteplirsen vs Natural History:
  - 4 Year
    - 6 Minute Walk Test (6MWT) & Loss of ambulation (LOA)
  - 3 Year
    - North Star Ambulatory Assessment
    - Ability to Rise Independently
- PFT/FVC % predicted: eteplirsen vs Published literature
“Reasonably Likely To Predict Benefit”

- Generally, correlation between dystrophin levels in muscle and disease outcome would be required.
- Regulatory flexibility utilized by FDA.
- The use of dystrophin as a surrogate endpoint, “reasonably likely to predict clinical benefit” was supported by:
  - Comparative clinical data (eteplirsen vs NH)**
  - Literature: small amounts of dystrophin are clinically meaningful.
    - DMD Exon 44 clinically milder phenotype¹⁻⁵
- Eteplirsen treatment goal is to slow disease progression.

Dr. Woodcock finds that using “…the greatest flexibility possible for FDA while remaining within its statutory framework,” etepliren is “…reasonably likely to predict clinical benefit.” Her conclusion is based on a view that the data from both Study 201/202 and Study 301 are from adequate and well-controlled trials and that, although imperfect, they adequately meet criteria to include as affirmation of a drug effect that is reasonably likely to predict clinical benefit. She points out the many uncertainties about extrapolating from a particular level of a surrogate to clinical benefit when that surrogate is not yet proven, including complexities of assay validation, determining whether protein is functional, and also the extraordinary difficulty of knowing how the amount of protein might affect functional outcome over time and within the context of the multidimensional nature of protein interactions in complex cellular and subcellular functions. She finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit. Furthermore, she provides some post-hoc calculations from the etepliren clinical trials that she regards as supportive, though not definitive, evidence that higher levels of dystrophin are associated with greater function.

She is clearly employing and interpreting the full range of appropriate information, comprising a “totality of evidence” approach in determining that the clinical trials demonstrated an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Because of the uncertainties in this situation with a surrogate that has not been validated, it is clear that Dr. Woodcock’s decision also utilized the flexibility afforded under the relevant statutory provisions, including consideration of the life-threatening nature of the disease and the lack of alternative treatments.
“Given the severity of the disease, the data obtained and the demonstrated safety of the product, the FDA made a difficult but correct decision that could encourage increased use of the Accelerated Approval pathway while maintaining FDA’s strong standards for safety and science-based decision making”

Emil Kakkis and Max Bronstein, EveryLife Foundation (https://morningconsult.com/opinions/closing-rare-disease-innovation-gap/)

“I recognize the objections to the Agency’s decision, but the FDA’s determination was grounded in both clinical data and the values and experiences of families affected by Duchenne, not public pressure. All the families reported eteplirsen slowed progression of the disease based on the aspects of function they value”

Marc Boutin, National Health Council (https://morningconsult.com/opinions/really-listening-patients/)
ESTABLISHED REGULATORY PRECEDENT
# Examples of Flexibility Of Rare Disease Drug Approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval Date</th>
<th>Basis For Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myozyme®</td>
<td>April 2006</td>
<td>Pivotal study of 18 patients; used natural history database to create a subgroup-matched historical control</td>
</tr>
<tr>
<td>Carbaglu®</td>
<td>March 2010</td>
<td>A case series derived from fewer than 20 patients and comparison to a historical control group</td>
</tr>
<tr>
<td>Ceptrotin®</td>
<td>March 2007</td>
<td>A study of 18 patients using a comparison to historical control data</td>
</tr>
<tr>
<td>Cresemba®</td>
<td>March 2015</td>
<td>A single-arm clinical trial of 37 patients compared with the natural disease progression</td>
</tr>
<tr>
<td>Cholbam®</td>
<td>March 2015</td>
<td>Trial 1. Non-randomized, open-label, single-arm trial in 50 patients over an 18 year period. Trial 2: an extension trial of 12 new patients along with 21 patients who rolled-over from Trial 1 (n=33 total)</td>
</tr>
</tbody>
</table>
<pre><code>                                       | Published case series of 15 patients.                                                                                                             |
</code></pre>
Thank you

Any Questions?
Accelerating the development of advanced diagnostic tools and effective treatments for systemic amyloidosis through collaboration and innovation
### The Systemic Amyloidoses Diseases

- Failure to recognize driven by rarity (3500 AL patients annually in US)
- Symptoms are vague with dozens of more common causes
- No single diagnostic blood test, or imaging study points to the correct diagnosis
- Even biopsies will overlook the presence of deposits if routine H & E screening is done
- Most types are fatal
- No FDA approved treatments

### Distribution of Amyloid types seen at Mayo Clinic

<table>
<thead>
<tr>
<th>Amyloid Subtype</th>
<th>Number (%) of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>2553 (61.68)</td>
</tr>
<tr>
<td>ATTR</td>
<td>1015 (24.52)</td>
</tr>
<tr>
<td>AA</td>
<td>151 (3.65)</td>
</tr>
<tr>
<td>ALect2</td>
<td>148 (3.58)</td>
</tr>
<tr>
<td>AIns</td>
<td>48 (1.09)</td>
</tr>
<tr>
<td>Keratin*</td>
<td>36 (0.87)</td>
</tr>
<tr>
<td>AApoA1</td>
<td>30 (0.72)</td>
</tr>
<tr>
<td>AH</td>
<td>27 (0.65)</td>
</tr>
<tr>
<td>AFib</td>
<td>26 (0.63)</td>
</tr>
<tr>
<td>TGFB1-IP*</td>
<td>22 (0.53)</td>
</tr>
<tr>
<td>AApoA4</td>
<td>20 (0.48)</td>
</tr>
<tr>
<td>AANF</td>
<td>14 (0.34)</td>
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<tr>
<td>Ab2M</td>
<td>12 (0.29)</td>
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<tr>
<td>AGe1</td>
<td>12 (0.29)</td>
</tr>
<tr>
<td>ASem1</td>
<td>12 (0.29)</td>
</tr>
<tr>
<td>APro</td>
<td>7 (0.17)</td>
</tr>
<tr>
<td>ALys</td>
<td>3 (0.07)</td>
</tr>
<tr>
<td>ACa1</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>Enfuvirtide*</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>AIAPP</td>
<td>2 (0.05)</td>
</tr>
</tbody>
</table>

Shown with permission from M. Gertz
Role of Patient Foundations in Drug Development Continuum

Valuable role in developing tools and support to accelerate drug development.

Reduce uncertainty over the benefit-risk-value.

Patients are experts in their disease, and properly engaged can play a vital role in all stages of drug development.
Building Programs to Support Drug Development

- Drug Development Round Table
- Educational Meetings
- Patient Focused Drug Development
- Guidance for Industry on Drug Development
- Biomarker white paper
- Additional publications
Types of Biomarker Studies Done by ARC

- Retrospective studies using clinical specimens, known clinical outcomes and research or analytically validated assays
- Prospective validation studies
- Exploratory (correlative) studies using clinical biospecimens and research assays
- Prospective natural history and biomarker studies
- Standardization of data collection across Collaborative Network
- Biobank
Role of NT-proBNP in AL amyloidosis

Clinical trials reporting that NT-proBNP response after intervention predicts clinical outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population (median age)</th>
<th>No.</th>
<th>Cardiac involvement %</th>
<th>Treatment Regimen</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palladini et al (2006)</td>
<td>No prior treatments (63 years)</td>
<td>51</td>
<td>100</td>
<td>MDex, T/Dex, Dex, MP, or T</td>
<td>&gt;80% at 40 months</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>13 months</td>
</tr>
<tr>
<td>Kastrits et al (2010)</td>
<td>Newly diagnosed and previously treated (62 years)</td>
<td>94</td>
<td>62</td>
<td>Bor, BDex</td>
<td>&gt;80% at 36 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 months</td>
</tr>
<tr>
<td>Palladini et al (2010)</td>
<td>Newly diagnosed (64 years)</td>
<td>171</td>
<td>37</td>
<td>MDex, CyTre, Dex, ASCT, &quot;other&quot;</td>
<td>&gt;80% at 60 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 months</td>
</tr>
<tr>
<td>Palladini et al (2012)</td>
<td>Newly diagnosed (63 years) Testing cohort 816</td>
<td>69</td>
<td>65</td>
<td>MDex, T-based, L-based, Bor-based, Dex, MP, ASCT, &quot;other&quot;</td>
<td>&gt;65% at 48 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 months</td>
</tr>
<tr>
<td></td>
<td>Newly diagnosed (64 years) Validation cohort 374</td>
<td>84</td>
<td>75</td>
<td>MDex, T-based, L-based, Bor-based, Dex, MP, ASCT, &quot;other&quot;</td>
<td>&gt;75% at 48 months</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>15 months</td>
</tr>
<tr>
<td>Kastrits et al (2015)</td>
<td>Newly diagnosed (57 years)</td>
<td>85</td>
<td>44</td>
<td>BDex, L-based, risk-adapted BDex</td>
<td>45 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 months</td>
</tr>
</tbody>
</table>


Prospective Data in Phase 3 Clinical Trials

- **NT-proBNP response (14 patients)**
- **NT-proBNP progression (19 patients)**

P = 0.049

Palladini et al, *ISA* 2016
Survival versus Biomarker: NT-proBNP

Merlini et al, Leukemia 2016
Biomarker Qualification Process Timeline

Timeline: Average 2-3 years

Adapted from FDA timeline
Summary

• Adequacy of biospecimen/imaging collection
• Funding for biomarker studies
• Regulatory requirements
• Inconsistency in data collection

Conclusion

• Cooperative groups have the capacity to conduct many types of biomarker studies, including formal validation trials
• Large numbers of patients are required for biomarker validation studies
• Commercial partners essential to meet regulatory requirements and support the costs of bio specimen analysis
Thank You!

To learn more about Community Congress and to join: www.everylifefoundation.org

Email: mbronstein@everylifefoundation.org