2016 Scientific Workshop #8
Evaluating Early Access Models for Patients: Flashpoints, Frameworks and Case Studies for Advancement

No Disease Is Too Rare to Deserve Treatment
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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
Policy and Advocacy Initiatives

Rare Disease Legislative Advocates educates and trains patients and parents on how to be effective in changing policy.

Expanding Newborn Screening state legislation to require a state to screen for a disease once it’s on the federal RUSP.

Community Congress fosters collaboration between patient organizations and industry representatives to seek policy solutions.

Incentivizing Rare-Repurposing federal legislation to double the number of rare disease therapies approved by FDA.
Workshop Series Topics

Designed to bring policy leaders together with experts in the field to build the scientific capacity needed to create science-driven policy solutions

- Workshop #1 Statistical analyses of rare disease studies
- Workshop #2 Clinical evaluation of rare disease treatments
- Workshop #3 Surrogate endpoints and accelerated approval
- Workshop #4 Developing Policy Recommendations for Accelerated Approval
- Workshop #5 Accelerated Approval in Rare Disease: Review of a White Paper Proposal
- Workshop #6 Rationalizing Safety Testing to Enable Clinical Studies and Approval in the US for Rare Disease Treatments
- Workshop #7 Incorporating the Patient Perspective in Rare Disease Drug Development

Find slides from prior workshops at www.everylifefoundation.org
Accessing the accelerated approval pathway for rare disease therapeutics

Emil D Kakkas, Sara Kowalczyk & Max G Bromstein

Improvements must be made to the qualification process for biomarkers as primary endpoints in pivotal clinical studies of treatments for the rarest of diseases.

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, multiclass 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 (44 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 lysozymal 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 paper2 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 is likely predicated on 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 guidelines for expedited programs, including accelerated approval3 and the Qualification Process for Drug Development Tools4, 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 diseases5 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 untreated 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 2000 to 2014 (refs. 6 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. Kakkis

Rare disease drug development could benefit substantially from increased patient involvement and 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 of incorporating the perspectives of patients. In the rare disease field in particular, the lack of quantitative understandings of disease burden and treatment outcomes means that patients are often under-represented in drug development. A comprehensive patient engagement approach, using primary interviews, focus groups, and patient surveys, can help construct potential impact scenarios and patient-centered evidence.

The study should get underway in five years, with the potential to affect drug development. This approach could not only influence new drug development but also improve access and affordability of existing therapies.

Figure S1 | Patient engagement during the drug development process. IND, investigational new drug.
Rationalizing Toxicology

- 2014 Scientific Workshop: Rationalizing Safety Testing to Enable Clinical Studies and Approval in the US for Rare Disease Treatments
- 2015: New FDA Guidance aligning US with EMA and significantly reducing tox data requirements

We Applaud FDA for Two New Draft Guidances on Rare Disease Drug Development

In May, the FDA outlined their new toxicology requirements for ultra-rare diseases in their draft guidance for industry, titled "Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment." The guidance potentially allows for only three months of chronic toxicology animal studies if there are no adverse findings, which is a significant improvement in policy. These changes are more in line with the applied European standards for entering clinical trials and are less than the traditional ICH guideline requirements for other non-native protein products. The Foundation worked to address this issue in our 2014 Scientific Workshop "Rationalizing Safety Testing to Enable Clinical Studies and Approval in the US for Rare Disease Treatments" and through our Cure The Process 2 Campaign. Longer toxicology requirements in the...
Goals for Today

Evaluating Early Access Models for Patients: Flashpoints, Frameworks and Case Studies for Advancement

- Early access is controversial
- A spirited, but *respectful* and *constructive* discussion is encouraged

**Agenda:**
- Origins and History
- Patient Navigators and Patient Experience
- Frameworks and Models
- Industry Case Studies
- Public Policy Landscape
- Small Group Discussions and Key Takeaways- Report Out to Larger Group

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