



DATE: Friday, October 16, 2015

TO: The U.S. Food and Drug Administration

RE: Docket ID: FDA-2015-D-2818-0001, Comments on Draft Guidance: “Rare Diseases: Common Issues in Drug Development”

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 Bozic, 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, Regeneron
- 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

Background & Introduction

The EveryLife Foundation for Rare Disease appreciates the opportunity to provide comments on the recently released guidance: *Rare Diseases: Common Issues in Drug Development Guidance for Industry*. To develop this commentary, the EveryLife Foundation assembled a working group through its Community Congress program, comprised of regulatory professionals from industry and patient

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group leadership. These comments do not necessarily represent the full views of the individual signing organizations, but rather a general consensus reached by the working group participants listed herein.

Substantive & Illustrative Examples Needed

Overall, the working group applauds the FDA for releasing this guidance as it represents a critical step toward providing needed guidance to industry. Rare disease drug development presents a variety of unique and at times, daunting challenges which may require significant guidance to overcome.

However, much of the guidance remains too general to substantially alter the status quo among organizations involved in rare disease drug development. In particular, specific illustrative examples would be constructive, especially in demonstrating how to overcome many of the challenges that come with developing drugs in the rare disease space (e.g. heterogeneity of populations, small sample sizes, resource gap for long-term studies).

Accounting for Ultra-rare Populations

Additional guidance is needed regarding smaller rare disease populations. Designing a clinical trial for a rare disease affecting 200,000 patients will be substantially different than a trial design for a disease affecting 1,000 patients or fewer. Providing guidance on addressing the unique challenges posed by ultra-rare diseases would be useful.

“I believe there needs to be some segmentation in the class 'rare diseases'. There is a huge difference in many aspects of a disease with a prevalence of 200,000 and one of 600, or 2000, or 10,000. There are several rare disease classes: including ultra-rare which we should seek FDA recognition for - beyond lumping all.”

- Jack Kelly, President, Lymphangiomatosis & Gorham’s Disease Alliance

“Given that rare diseases (which number around 7,000) are heterogenous across many characteristics (e.g., size of prevalent population, acute vs. chronic, young vs. elderly, singular diseases vs. multi-organ system involvement, disease severity, indolent vs. aggressive, no therapy vs. multiple therapy options), I would advise the FDA to provide regulatory perspective and guidance for major subgroups within rare diseases since the guidance is likely to differ.”

- Badri Rengarajan, MD, Special Project Contributor, International Pemphigus & Pemphigoid Foundation

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Natural History Studies

The working group agrees that natural history studies are useful for gaining a sharper understanding of rare diseases, but there are a variety of challenges that may make these studies impractical. For many of the companies engaged in rare disease drug development, resource constraints may make a multi-year natural history study a cost-prohibitive endeavor. The level of expertise that is needed to accurately diagnose and follow patients with rare and especially ultra-rare diseases is in short supply and many clinicians may be geographically distant from a patient population. In addition, undertaking long-term studies does little to address the acute needs of most rare disease patients who are urgently seeking treatments.

“While the symptoms of pityriasis rubra pilaris (PRP) are universal among patients, they will vary dramatically from patient to patient. A Natural History Study about an über rare disease, therefore, must address the sequence, duration and severity of each symptom.”

- Bill McCue, Founder & CEO, PRP Alliance

“The FDA needs to indicate that a cross sectional view of the patient registry might provide adequate information that would help in study design with the appropriate endpoints. It is very difficult to start a natural history study and follow up with patients for years to establish a longitudinal data set.”

- May Orfali, Global Medical Lead, Rare Disease Unit, Pfizer

Use of Biomarkers

Clear guidance on the evidentiary standards needed to qualify biomarkers is urgently needed. The FDA should set out scientific standards for use of biomarkers in rare disease drug development and in what instances biomarkers can be used as surrogate endpoints. This is especially critical in situations where common disease metrics are difficult or impossible due to sample size, population heterogeneity, or the time frame of disease progression. In addition, examples of validated biomarkers for specific rare diseases or disease pathways would be a useful guidance for developers.

“Still missing is a stronger statement about how to overcome the uncertainty that comes with very small patient populations, and the use of biomarkers as endpoints. The guidance leaves us hanging as to how to get drugs developed sooner. Done well, natural history data collection takes many years as we measure the long-term progression of disease. In the meantime, we need short-term solutions that use biomarker endpoints, genetic, and clinical data.”

- Steve Smith, Chief Patient Advocate, Medidata Solutions, & MPS Parent Advocate

“The need is urgent as the duration of clinical trials is insufficient to see the potential impact of a given compound or biologic. Biomarkers would provide significant insight into biological activity as well as encourage industry to consider developing protocols that include individuals across the spectrum of the disease of interest. Without this, most patients with rare disease will see possibilities for therapies but have few opportunities for access.”

- Patricia Furlong, President, Parent Project Muscular Dystrophy

Flexibility & Alternative Trial Designs

In addition to natural history studies, there are other mechanisms by which valuable data can be gathered about disease progression that could be useful in establishing disease endpoints. Cross sectional, no-drug studies, for example, may be a viable alternative to traditional natural history studies, which previously noted above, may be infeasible for many rare and ultra rare diseases. Furthermore, guidance should be provided on creative and/or alternative study designs like open label studies with blinded assessments.

“The endpoint that is most likely to demonstrate clinical benefit may not always be predictable when starting a trial. Multiple comprehensive endpoints, with complete patient history, is important to assure that the study can provide insights into potential benefits. Given the limited number of patients with many of the rare diseases, this can provide a positive result that might not have been predicted and subsequently benefit patients.”

- Lynne McGrath, Vice-President, Regulatory Affairs, RegenxBio

“The FDA should raise the use of larger cross-section no-drug studies to help establish endpoints and gain disease information to support a drug clinical trial, and recognize that natural history studies are expensive and require time and expertise that is often not available.”

- Emil Kakkis, President, EveryLife Foundation for Rare Diseases

Conclusion

This guidance represents an important step forward for the FDA and for stakeholders involved in rare disease drug development. However, much of the information provided in the guidance may be too general to substantially advance drug development efforts. The final guidance should include examples that Sponsors may draw upon along with more specific information for the unique challenges faced by those seeking to develop treatments for ultra rare diseases. Again, we are appreciative for the opportunity to comment and look forward to the final guidance.

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