FDA Updates Draft Guidance on Rare Diseases
Some Key Takeaways You Need to Know

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In January 2019, the US Food and Drug Administration (FDA) released new draft guidance on rare diseases (*Rare Diseases: Common Issues in Drug Development, Guidance for Industry*[1]), which replaces the guidance on rare diseases previously released in 2015 (*Rare Diseases: Common Issues in Drug Development*, August 2015). Since rare diseases are a fast-growing and important target for new drug development, some of the key implications of this guidance for pharmaceutical companies developing products for this context of use are outlined below.

Rare diseases were defined in the Orphan Drug Act (ODA) of 2010 as diseases that affect fewer than 200,000 patients, although many of them afflict far fewer numbers. Several factors contribute to the challenges of bringing new drugs to market for these diseases, including: a) they are predominantly up to 75% diseases that afflict children; b) very small sample sizes available for studies create challenges in using traditional statistical and study design methodologies; and, c) considerable clinical challenges – such as unique symptom clusters, or symptoms that may mimic other diseases – thus making diagnosis difficult. Traditional methodologies for validation and statistical analysis are particularly challenged. An excellent introduction to the general issues for outcomes researchers in rare diseases can be found in the ISPOR COA Good Practices Task Force Report on Rare Diseases (Benjamin et al., 2017).[2]

This article highlights several topic areas from the new draft guidance that may be of particular interest to outcomes researchers and drug developers.


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1. **The importance of protocol-driven, prospective, natural history studies is emphasized,** and since there is often not a great deal known about rare diseases, these studies are particularly relevant. Understanding the natural history is essential to:
   a. Defining the disease population to be studied
   b. Selecting the appropriate outcome measures
   c. Helping establish study design parameters such as length of follow-up and frequency of evaluation
   d. Developing biomarkers

   One passage in the discussion of rare diseases (lines 151-155) is particularly pertinent to patient-centered researchers in helping to identify "signs and symptoms that are most important to patients." It goes on to make a related point, which is that it is important to "collect … reports of patient functioning and feeling." An example of this type of work can be found in a recent publication about the adaptation and validation of a new measure of functional outcomes in the rare disease Pantothenate Kinase-Associated Neurodegeneration (PKAN) based on UPDRS-2, originally developed for Parkinson's Disease. (Marshall et al., 2019).[3]

   (For more information, see "Natural History Studies in Rare Diseases and Genetic Biomarkers" by Bevan et al. and "Registries in Rare Disease Research – Approaches to Optimize Success" by Ross in this issue of *The Evidence Forum*.)

2. **Issues of study design are raised.** Although the guidance does not specifically mention statistical or design issues, referring the reader to previous guidance published by ICH (*E9 Statistical Principles for Clinical Trials* [September 1998] and *E10 Choice of Control Group and Related 77 Issues in Clinical Trials* [May 2001]), special considerations are required to statistically analyze and make robust inferences about data from very small samples. The guidance does mention that in some cases, such as when it may be unethical to have a placebo arm, a well-designed natural history study can serve as an external control for a clinical trial, a very pragmatic recommendation in this setting (lines 140-141). The guidance also suggests that adaptive designs which allow data collected early in the study to be used later in the study may be applied under certain circumstances (lines 419-424).

3. **Given small sample sizes, it can be essential to use well-known outcomes measures where possible** (preferably those with norms developed for their use, or at minimum responder definitions to help interpret the meaning of scores). An example of this can be found in a recently published, cross-sectional burden of illness study in another rare disease (hATTR-FAP) (Stewart et al., 2018).[4]

4. **Adaptation of clinical outcome assessments (COAs) are suggested.** Since many rare diseases may have certain aspects that are similar to other more common diseases, even though the underlying metabolic pathway may be quite different, outcomes researchers may be involved in adapting existing COAs for a new context of use, rather than developing new instruments, as in the work cited above by Marshall et al.[4] (Also see "Adapting an Existing Instrument for a Rare Disease – A Valuable Resource within Your Reach" by Murray and Bacci in this issue of *The Evidence Forum*). Clinical outcomes rather than surrogate markers remain the most common way with which drugs are evaluated (lines 400-402).

5. **The Agency suggests several ways to improve the reliability of assessment and diminish the possibility of bias in clinical evaluations,** including rater training, and even blinded, centralized ratings (lines 445-451).

6. **Safety evaluations** may, in certain conditions, be facilitated through direct, systematic reports from patients, as is being done increasingly in oncology studies, for example, using the Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) (Basch et al., 2014[5]; Speck et al., 2018[6]).

7. **Finally, the role of direct engagement with patients with rare diseases** can greatly facilitate both scientific accuracy and operational efficiencies in terms of identifying outcomes meaningful to patients and finding patients willing to participate in experimental studies. In lines 728-730, under Additional Considerations, the FDA recommends direct communication between sponsors and patients regarding "potential endpoints and meaningful changes."

Treatments for rare diseases continues to grow at a rapid rate, with more than 600 orphan drugs being approved by the FDA since the passage of the Orphan Drug Act in 1983, and 560 medicines in clinical development for the treatment of rare diseases.[7] And while there are over 7,000 different rare diseases that have been identified to date, only 5% of those diseases have treatments.[7,8] With 350 million people suffering from a rare disease globally,[8] the emphasis on developing treatments for these indications has grown significantly. In the US, 41% of all new medications approved by the FDA in 2016 were orphan drugs to treat rare diseases,[9] and in the EU, 1,900 medicines were granted orphan status by the end of 2017, with 140 orphan medicines marketed in the EU as of August 31, 2018.[10]

The FDA's updated draft guidance on rare diseases indicates a continued interest in providing sound recommendations in support of providing a way forward for companies developing treatments for those suffering with rare diseases. FDA Commissioner Scott Gottlieb, MD, recently stated "The FDA is committed to supporting the development of treatments for patients with rare diseases and has been focused on advancing policies that will help enable these opportunities. We know that developing a drug or biologic for a rare disease can be especially challenging, which is why it's important that the FDA continues to provide clear information to drug developers so that they can plan modern, efficient drug development programs that will be successful."[11]

The guidance also aligns with FDA's commitment to more patient-focused drug development with the inclusion of several points related to patient outcomes, COA adaptation, and direct patient engagement. There are some very important issues addressed in the updated draft guidance that are very relevant to, and supportive of, early evidence planning, inclusion of the patient perspective, and real-world studies to supplement clinical data – all of which can be vital aspects of a complete evidence package that is often unique to rare disease treatments receiving regulatory approval and market access. ■

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