Rare Diseases and FDA Advisory Committees: **Be the Experts in the Room**

"When it comes to advisory committees that are convened for rare diseases, everyone must become an 'educator'. This includes the applicant, external experts and open public hearing participants."

By definition, a disease is considered rare if it affects fewer than 200,000 people in the United States. However, an estimated one in ten Americans has a rare disease and about one third of all new drugs approved by FDA are now for rare diseases [1]. In fact, in 2017 the FDA approved a record 80 new treatments for rare diseases [2].

Whenever an FDA advisory committee is convened as part of the approval process, the stakes are high and there can be communication challenges. However, for applicants preparing for an advisory committee that is for a rare disease, the challenges are unique. This paper outlines some of those challenges, along with key factors for success.

Key Challenges

Advisory committee members

Due to their very nature, rare diseases are not generally well understood by advisory committee members. In fact, there may be very few experts worldwide who understand the disease. This issue is compounded when rare diseases are treated using a multi-specialty approach since advisory committees are generally organized by therapeutic areas (e.g. cardiology, oncology, gastroenterology, etc.). Although FDA invites temporary members to meetings to help round out the experience of the permanent roster, the advisory committee inevitably includes a fair number of members who are 'naïve' to the disease area.

Benefit/risk assessment

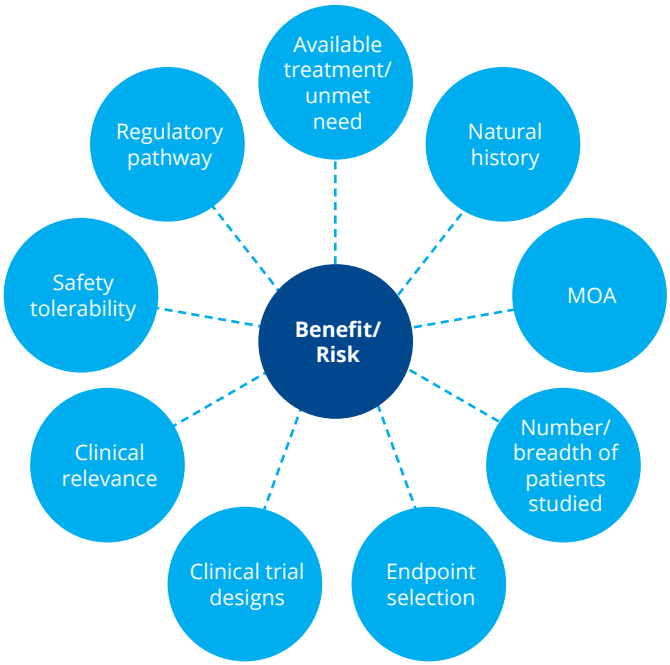
Key factors for assessing benefit/risk are shown in the diagram below *(figure 1)*. While the concepts are common across diseases, they pose unique challenges for advisory committees that are convened for rare disease treatments.

- *Available treatment/unmet need*
  Even when there may be agreement that there is a high unmet need, current standards of care may not be well understood. In addition, there may be wide variations in those standards across the regions in which the clinical trial program was conducted.

- *Natural history*
  Lack of understanding of the natural history of a rare disease can be a key stumbling block. Natural history studies or registry analyses are typically limited and even when they exist, heterogeneity of a rare disease can complicate their interpretation.

- *Mechanism of action (MOA)*
  Often the mechanism of action may be novel and highly targeted, as is the case with precision medicines. When a product is first in class, there may be concerns regarding the validity of the pharmacodynamic endpoints that are being used to demonstrate proof of concept. Concerns may be compounded if there is a lack of consensus around the underlying disease pathophysiology.
- *Number/breadth of patients studied*
  Given that there are a limited number of available patients for rare disease evaluation, the size of the clinical program is usually much smaller than what an advisory committee is used to seeing. When there is heterogeneity in the population (e.g. in terms of disease characteristics and/or standard of care), sample size concerns are exacerbated, and extrapolation of results can become a major issue.
- *Endpoint selection*
  Committee members may not fully understand the rationale for the endpoints selected, their clinical relevance, how they are measured or how they are standardized for clinical trials.
- *Clinical trial designs*
  It is common for rare disease programs to include only one Phase 2b or Phase 3 trial. These trials may be open label and there may be novel design elements. This can be a source of significant concern when the committee interprets results, especially when p-values are >0.001.
- *Clinical relevance*
  Even with robust clinical efficacy data, the clinical relevance of the results may not always be obvious to the committee given their lack of familiarity with the rare disease.
- *Safety and tolerability*
  Safety and tolerability data may be questioned due to limitations in the sample size and trial length. Concerns may arise regarding the ability of the dataset to capture serious, rare safety signals that may emerge over time. And, again, interpretation may be complicated by a lack of understanding of the natural history.
- *Regulatory pathway*
  Committee members are generally clinicians and not regulators. As such, they can be uncertain about whether and how to apply regulatory statutes (e.g. FDASIA) that provide for flexibility around rare diseases. For this reason, they may be more influenced by how FDA views the application and be less willing to challenge the agency.

Figure 1.
Benefit/Risk assessment for rare diseases.



Key Factors for Success

Advisory Committee Research

Start by understanding the audience. What is the committee's composition? What meetings have been held? How many were for a rare disease? Importantly, how were the questions to the committee structured by FDA? What issues were raised in Q&A?

Issue Identification

Align on the key issues. What key issues did FDA raise in your previous meetings and correspondence? What concerns might the committee have related to Benefit/Risk assessment?

Messaging Strategy

Develop a clear, concise and compelling messaging strategy. What key messages will you need to communicate in your briefing materials, presentation and responses to questions in order to address the issues identified?

Speaker Strategy

When it comes to advisory committees that are convened for rare diseases, everyone must become an 'educator'. This includes the applicant, external experts and open public hearing participants. Who are the best people to communicate the key messages from your company and how can external experts help?

Preparation + Practice (and More Practice)

It is important to 'never ad lib and ad com'. The stakes are too high. Thorough preparation is critical, including the use of mock panels that are representative of the likely advisory committee roster and expert leadership of the overall process.

For more information on how we can help your team 'Prepare to Win' please contact **info@ndareg.com**
Rare disease case examples and a copy of our general 'Introduction to Advisory Committees' paper are also available upon request.

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Principal Neelu Agrawal has over 25 years of strategic communication, management consulting and cross-functional leadership experience. She has worked closely with clinical, regulatory and commercial teams across all stages of the product lifecycle in over 30 product categories.

She is an expert in high stake meeting preparations, including FDA Advisory Committees, Oral Explanations, and Scientific Advisory Groups.

References:

(1) NORD. Rare Disease Facts

(2) 'Taking New Steps to Meet the Challenges of Rare Diseases – FDA Marks the 11th Rare Disease Day', Gottlieb; FDA Voice; February 26, 2018