The Evidence Requirements for Orphan Drugs From a Payer Perspective: Is the Bar Raised or Lowered?

Karen Sandman, PhD, U.S. Practice Lead, Payer Communications, Evidera

This issue includes discussions on a variety of methodologies to study epidemiology, patient-reported outcomes, comparative effectiveness and healthcare decision-making in rare diseases. One question that comes to mind is, "Do we need all this? If a disease is rare enough, and severe enough, doesn't the unmet need speak for itself?" If only it were so easy! As anyone who has worked in rare diseases in the past decade can attest, the "glory days" of easy market access for orphan drugs — if they ever existed — are over.

Certainly, there are many healthcare systems, such as those in Germany and Australia, that evaluate treatments for orphan diseases differently than those for more common conditions. Most payers recognize that orphan drugs have high prices because the cost of developing the drug and keeping it on the market is not proportional to the size of the target population, and manufacturers need to price sufficiently high to maintain profitability — and thus to be able to provide the drug to the patients who need it. Despite understanding the unique aspects of orphan diseases, payers also are managing finite healthcare resources, and there has been a steady uptick in the number of orphan drugs on the market in recent years.

The balance between the desire to provide equitable treatment to patients with rare diseases and the need to contain healthcare spending leads to a set of evidence requirements for orphan drugs. The core principles of market access apply regardless of the disease: The manufacturer needs to make a clear case for burden of illness, unmet need, clinical efficacy and safety, comparative effectiveness, patient-relevant outcomes and economic value. Let's take a look at some typical objections raised in the case of rare diseases and how evidence might help to address payer concerns.

How solid are your prevalence estimates? How do I know the target population is not going to creep up to higher levels, especially now that the awareness will be higher and there may be more diagnostic testing?

Manufacturers often communicate to payers that the budget impact of an orphan drug will be low based on the very small size of the target patient population. For this economic argument to be compelling, however, there must be strong confidence in prevalence estimates. Getting solid epidemiology figures in rare diseases can be challenging, and oft-cited literature-based estimates may be based on outdated data or questionable assumptions. For maximum credibility, it is advisable to use current, scientifically rigorous prevalence estimates, particularly when these estimates will support an economic analysis.

Another emerging issue is related to genetic testing. Many rare diseases are genetically based, and there can be a broad range of disease severity depending on the specific genetic variant that a patient has. With increased disease awareness and the broader availability of genetic testing, there may be more patients genetically diagnosed with a rare disease who would not have been diagnosed according to standard clinical criteria. Payers may therefore be concerned about the potential for the target population to creep up to higher prevalence levels, with increasing budget impact. In these situations, it is critical to reinforce the commitment to appropriate use. Prospective observational studies of patients with less severe phenotypes may help to establish the disease burden and better elucidate appropriate treatment for these patients.

The standard of care in this disease is "watch and wait," and I am not convinced that patients need a more aggressive treatment approach.

For many rare diseases, the standard of care has been defined not by evidence-based medicine, but by the lack of suitable treatment options. Despite evidence demonstrating the efficacy and safety of a new product, there may be a perception that patients do reasonably well without active treatment.

To address this perception, it is necessary to assess the true clinical burden and unmet need in the rare disease. Perhaps disease pathology occurs much earlier in the patient's life than had been thought, and the process could be prevented or slowed by appropriate disease-modifying treatment long before the onset of severe signs and symptoms.

In some cases, a careful and comprehensive review of the literature will provide sufficient evidence on disease progression. In other cases, a detailed chart review or other type of real-world study can reveal the true clinical burden and unmet need in a rare disease. Disease simulation models can also be useful tools to correlate disease pathology with long-term clinical consequences.

The efficacy data are limited to 1 year. We need longer term data to evaluate the benefits and risks of this treatment.
ager to bring an effective product to patients with limited treatment options, orphan drug manufacturers often submit relatively short-term data for regulatory approval. While some payers will reimburse based on shorter term results, others may expect longer term data before making a final coverage decision.

Certainly, extension studies and registries can provide the longer term efficacy data being sought. To the greatest extent possible, the long-term extension studies and registries should include payer-meaningful outcomes such as resource utilization, patient-reported outcomes and long-term safety.

You are showing me efficacy based on an endpoint that I can't correlate to real life. Does this endpoint translate to increased survival? Decreased resource utilization? Pain reduction or improved quality of life?
Orphan drugs may receive approval based on a biologically relevant, surrogate endpoint that is clearly correlated to the product's mechanism of action. While this makes great scientific sense, payers want to use their resources to treat patients, not proteins. Ideally, the pivotal trial should be designed to capture outcomes that are meaningful from a clinical, humanistic and economic point of view.

If the pivotal trial has already been designed and the endpoints do not cover all of the relevant topics, there is a need to connect some dots. Can you use real-world evidence to show the correlation between the trial's primary endpoint and some more meaningful outcomes? Would patient interviews or vignettes demonstrate the relevance of the surrogate endpoint? Ultimately, the payer needs to feel confident that the drug's value can be measured in patient-relevant terms, and this information is also critical for developing a robust economic analysis.

The economic analysis is not sufficiently robust: The inputs of the model rely on assumptions that are inadequately justified (e.g., utility values, survival benefit, likely underestimate of costs, assumptions regarding the product alleviating the need for other standard supportive treatments).
Ultimately, if there is a strong base of evidence relating to burden of illness, unmet need, clinical efficacy, safety, comparative effectiveness and patient-relevant outcomes, then it should be possible to develop a robust and credible economic analysis of the treatment of an orphan disease. As outlined earlier in this article, there are places where all of these types of evidence can fall short, especially in the case of orphan diseases, where literature may be sparse and available patient data may be limited. By taking a proactive and thoughtful approach to building the evidence dossier for an orphan drug, it should be possible to support a compelling value proposition.

So … is the bar raised or lowered?
Getting back to the original question: Is the expectation for evidence supporting an orphan drug higher or lower than that for products used in more common diseases?

IDEALLY, THE PIVOTAL TRIAL SHOULD BE DESIGNED TO CAPTURE OUTCOMES THAT ARE MEANINGFUL FROM A CLINICAL, HUMANISTIC AND ECONOMIC POINT OF VIEW.

Instead of having to differentiate a product in a crowded primary care market, often with generic competition, manufacturers of orphan drugs are faced with the challenge of finding difficult-to-obtain evidence, which requires a good deal of planning and foresight. Ultimately, though, payers are looking for the same types of evidence regardless of how many patients are affected by the disease: Does this product safely and effectively address an unmet medical need, and is its cost acceptable within the constraints on how we spend our healthcare funds? I don't think the bar is necessarily higher or lower for orphan drugs, but perhaps it is zig-zagged, with some areas more challenging and others less so.

For more information, please contact Karen.Sandman@evidera.com.