Evidence Requirements for Orphan Drugs from a Payer Perspective

How Can Early Scientific Advice Help?

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This issue of *The Evidence Forum* includes discussions on a variety of methodologies that can be used to understand, characterize, and document unmet need and product value 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, therefore, be able to provide the drug to the patients who need it. Despite understanding the unique aspects of orphan diseases, payers are managing finite healthcare resources, and there has been a steady uptick in the number of orphan drugs on the market in recent years.

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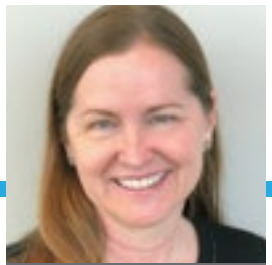

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The balance between the desire to provide equitable treatment to patients with rare diseases and the need to contain healthcare spending can lead to unique challenges in demonstrating the value of orphan drugs. The core principles of market access 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. In the case of orphan drugs, however, evidence may be scant, or it may be necessary to provide additional context for the available evidence.

In general, teams who are preparing to launch drugs in orphan indications have strong awareness of the level of evidence needed to support their product's value proposition, but for any number of reasons their evidence package often falls short in one or two key areas. The two main reasons tend to be that:

- The market access and HEOR teams are not involved early enough in the process – often because the product was acquired close to launch
- Those responsible for the pivotal trial design are unaware or skeptical of the need for payer-relevant endpoints, such as healthcare resource utilization and a validated, disease-specific measure of health-related quality of life

One way to preemptively address these issues is to seek Early Scientific Advice, in which manufacturers can consult with regulators and health technology assessment (HTA) bodies regarding the types of clinical and HEOR evidence that would be necessary and sufficient to support regulatory approval and market access (See Table 1). Unlike a purely regulatory consultation, Early Scientific Advice engages with market access experts to obtain input on the types of evidence that would be most supportive during the HTA process. Early Scientific Advice, which is non-binding, can come from a single HTA authority, such as the G-BA (the Federal Joint Committee) in Germany or NICE (National Institute for Health and Care Excellence) in the UK, or it may include multiple HTA bodies, in the context of EUnetHTA Multi-HTA Early Dialogues or EUnetHTA/European Medicines Agency (EMA) Parallel Consultation.

A manufacturer should plan ahead to engage in Early Scientific Advice as it may take about six months to prepare for the process, which should occur during Phase II. Ideally, there should be time for clinical development and market access teams to consider how to apply the advice to the Phase III trial design and to additional studies to address payer evidence gaps.

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? With Early Scientific Advice, the manufacturer has an opportunity to discuss with decision makers before finalizing the evidence generation plan, to ensure that the studies ask and answer the most relevant questions. ■

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Table 1. Key Questions Addressed in Early Scientific Advice … and How They Relate to Orphan Drugs

Study Population/Indication

- What will the patient population be in real-world practice? How will clinicians identify patients?
- How is the population defined in trials, and how might payers react when making coverage and reimbursement decisions?
- How might inclusion/exclusion criteria impact generalizability of results for payers?

How solid are your prevalence estimates?

- Manufacturers often state that the budget impact of an orphan drug will be low based on the very small target patient population.
- For this economic argument to be compelling, there must be strong confidence in prevalence estimates.
- For maximum credibility, it is advisable to use current, scientifically rigorous prevalence estimates, particularly when these estimates will support an economic analysis.

How do I know the target population is not going to creep up to higher levels, especially now with increased awareness and potentially more diagnostic testing?

- 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 be concerned about the potential for the target population to expand to higher prevalence levels, with increasing budget impact.
  - 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.

Study Design

- Are the endpoints appropriate for both regulators and payers?
- Is the study of adequate duration? How important is long-term follow-up?
- Are the planned subgroup analyses sufficient for payers? Which must be powered, and which subgroup analyses should be planned but not powered?

The efficacy data are limited to one year. We need longer-term data to evaluate the benefits and risks of this treatment.

- Eager to bring an effective product to patients with limited treatment options, orphan drug manufacturers often submit relatively short-term data for regulatory approval.
- Extension studies and registries can provide the longer-term efficacy and safety data being sought.
- Long-term extension studies and registries should include payer-meaningful outcomes, such as resource utilization, patient-reported outcomes, and long-term safety.

There is no active comparator (or there is no comparator at all) in the registrational trial.

- Often in a rare disease, there is no acceptable active comparator, and when the unmet need is large, it may be considered unethical to conduct a placebo-controlled trial.
- An indirect treatment comparison may be useful in lieu of a head-to-head clinical trial, but this depends on the availability, quality, and relevance of published trials of other treatments.
- It is essential to be upfront and clear about appropriateness of the trial design for an orphan drug.
- Keep the message focused on efficacy benefits in a disease characterized by substantial burden and unmet need.

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.
- 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 the relevant topics:
  - Can real-world evidence correlate the trials' primary endpoint with some more meaningful outcomes?
  - Would patient interviews or vignettes demonstrate the relevance of the surrogate endpoint?

Comparator/Standard of Care

- What is the standard of care from the HTA perspective?
- What would need to be shown to differentiate the product from the standard of care?

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, standard of care has been defined by the lack of suitable treatment options, leading to the perception that patients do reasonably well without active treatment. It is necessary to establish the true clinical burden and unmet need, including consequences of untreated disease progression, in the rare disease.
- A careful and comprehensive review of the literature may provide sufficient evidence on disease progression.
- 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.

Evidence Gaps

- What evidence not captured in trials may be needed for HTA?
- Is there a need for observational studies, registries, long-term extensions?
- Is the planned approach for collecting/using health economic data acceptable? What is missing?

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.
  - There are places where all 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.