

Valuing Your Orphan Drug with Appropriate Evidence: Prepare Well and Get the Perspective Right

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INTRODUCTION

As more rare and debilitating diseases are identified, the need for new orphan drug innovations to tackle these conditions becomes more in focus. This is recognized by the increases in both market share and prescribing levels of orphan drug technologies over recent years.¹ However, impact on budgets of these orphan drugs is a growing concern for policy makers and payers.

To this end, decision makers are demanding greater quantities of evidence with an increasing level of scientific rigor^{2,3} to demonstrate comparative effectiveness. In general, the high cost of orphan drugs is often in conflict with the perceived benefit of the product in relation to any alternative treatment and the consumption of the healthcare resource budget, given that rare diseases affect so few people.

Furthermore, competitive challenges among the crowded therapeutic marketplace have driven the need for not only greater payer scrutiny but product differentiation and comparative assessments.

Obtaining optimal product positioning and market uptake requires manufacturers to address the issues that will define product value. What is fundamental to this goal is generating robust, demonstrable evidence that is:

- At an appropriate depth and quality
- Relevant for the particular audience
- Produced at the most appropriate time in the product life cycle development

This is no different for orphan products targeting rare diseases. However, while many of these principles are well tested for non-orphan drugs, demonstrating the value of an orphan drug can be challenging from the various decision-making standpoints — policy makers, payers, patients and providers.

EVIDENCE CHALLENGES

Payer sensitivity is growing and this is understandable. Often questions are raised around the quality and appropriateness of the evidence to back up any value claims; economic models use assumptions based on this evidence, and hard endpoints such as health-related quality of life data may be missing. This creates greater uncertainty from the payer's perspective.⁴ Additionally, payers have become increasingly skeptical if orphan drugs are initially reimbursed for a specific disease and later are extended to non-orphan indications. The result is payers often apply greater restrictions to orphan drug use, and it is suggested there is a clear correlation between lack of sufficient evidence and reimbursement rejection rates by payers.⁵

The *nature of the evidence* used to demonstrate value provides a wide range of challenges. Burden of illness and the level of unmet need may be difficult to establish as the natural history of the disease and definitions of rare conditions are not always clear. Data may be limited to only a few individuals with the condition. Linked to this, questions are raised about single-arm clinical

trial designs, the choice or lack of appropriate comparators and the need to measure surrogate endpoints across short time horizons. There may be limited evidence on survival, function or feelings of individuals who live with rare diseases. Similarly, with these limitations in evidence, demonstrating cost-effectiveness and measuring the full impact on healthcare budgets is challenging.

Decision-maker assessment approaches to orphan drugs in different markets are not necessarily equivalent.⁶ Some payers apply the same evaluation criteria to those they apply to non-orphan drugs (National Institute for Health and Care Excellence [NICE] or Scottish Medicines Consortium [SMC] in the UK, for example). Others adopt different criteria to recognize the differences in orphan drug value propositions (the Federal Joint Committee - Gemeinsamer Bundesausschuss [G-BA] in Germany, for example). Classification of an orphan drug varies between countries, primarily based on size of target population. Some assessments are fast tracked, whereas others are evaluated using currently established and thorough appraisals. Countries using evaluation methodologies such as cost-effectiveness (cost per quality of life year) could struggle to demonstrate the true value of orphan drugs as these approaches may not be sensitive enough to assess the budget impact and wider health gain on patients and their caregivers.

Targeting the evidence generation activity is an important consideration for manufacturers. Given the difference in payer approaches, early dialogue with key opinion leaders (both from a clinical and reimbursement perspective) in each market will be key in guiding decisions around the right evidence needed for the right audience at the most appropriate time. This will crystalize any plan to generate evidence, adopting the right balance and focus of evidence. For instance, some payers will favor a stronger underpinning argument around the clinical effectiveness of an orphan drug product in a particular indication. Others will need to see both cost and

clinical effectiveness comparisons to current standard of care.

EVIDENCE REQUIREMENTS IN VARIOUS MARKETS

The table below represents a practical approach for manufacturers to begin to appraise their position with regard to the evidence requirements in any particular market. Early dialogue with payers and other key opinion leaders will help to detail the right evidence for the right audience at the appropriate time.⁷ It will be clear if the data and other evidence that manufacturers have at their disposal matches the key requirements for future payer decision making.

GENERATING THE RIGHT EVIDENCE FOR THE RIGHT AUDIENCE IS A SYSTEMATIC AND EVIDENCE-BASED PROCESS.

Table 1: Example of how a manufacturer might develop an evidence framework for its product

Decision maker criteria in target market	What evidence is needed / appropriate?	What evidence is available now?	What are the evidence gaps?	What studies should be undertaken to fill the gaps?	Timings or associations	Strength of argument / position
Burden of Illness / unmet need						
Clinical value						
Economic value						
Outcomes value						
Unique HTA requirements						

SYSTEMATIC AND EVIDENCE-BASED APPROACH TO DEMONSTRATING VALUE

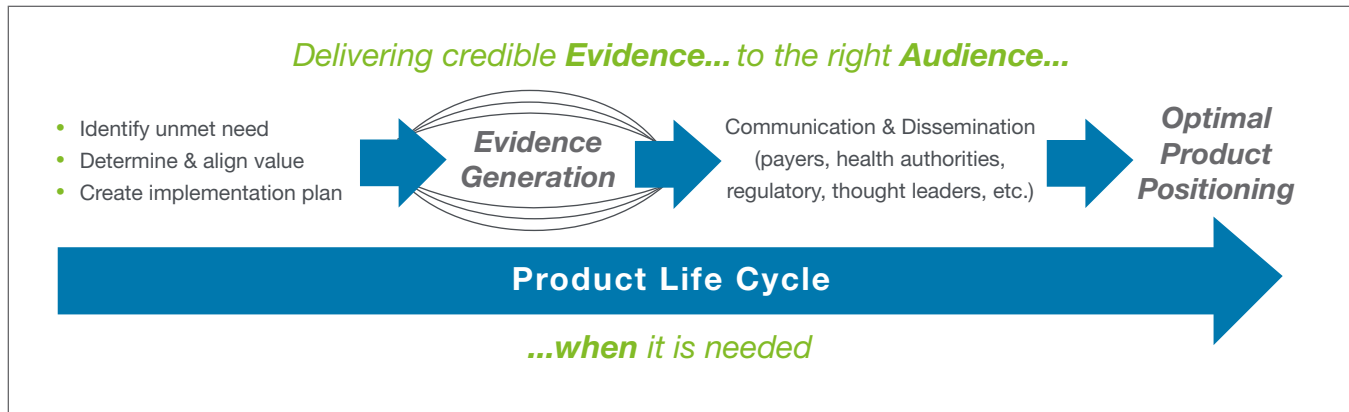
The approach to determining the value of a drug with orphan status is equivalent to that of non-orphan drugs, even if the nature and balance of the evidence required may vary in different markets. Generating the right evidence for the right audience is a systematic and evidence-based process whereby manufacturers need to:

- Understand what the burden of the rare disease is and what needs to be the product value focus, given the target market and payer evaluation process
- Understand what evidence is required, to what detail, and what is currently available within the organization and how any evidence gaps should be filled
- Design and develop appropriate, defensible and tailored value messages for each market

SUMMARY

Manufacturers need to remember that there may be a requirement for greater evidence generation investment in the rare disease space, both before and after product launch. They will need a greater understanding of payer responses to different levels of the value story. To this end, early engagement in constructive dialogue with payers and other orphan drug stakeholders is recommended, together with earlier involvement of HEOR activity in the

Figure 1: Illustration of evidence planning approach for orphan and non-orphan drugs



evidence generation process, e.g., development of patient-reported outcomes (PRO) instruments and defining and agreeing on meaningful, patient-centered endpoints to inform trial design and economic model parameters.

Earlier commentary on orphan drug reimbursement decisions suggests that different value messages (or combinations of) may be more appropriate and should underpin any developing evidence and market strategy. For example, clinical effectiveness evidence, impact on

clinical practice or patient outcomes, or detailed budget impact may be more appropriate than cost-effectiveness comparisons alone. There is also recognition that the traditional evidence base associated with drugs with non-orphan status may need to be supplemented by strong arguments around clinical effectiveness and patient equity/access in the orphan drug arena. This has additional implications for orphan drug pricing given the level of reimbursement support for individual patients locally.

Finally, effectively addressing these issues requires a comprehensive, multiyear, multidimensional strategy to document and communicate evidence of product value. The key is to be creative while establishing a standardized and consistent value demonstration methodology as part of an orphan drug product strategy. This will facilitate and optimize coverage, reimbursement and market adoption.

For more information, please contact Jeff.Anderson@evidera.com.

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