Executive Briefing #7

Early Market Access – Value Demonstration Based on Less Complete Data

David Schwicker, February 2017

Innovative and transformative medicines continue to command higher prices, in the case of orphan drugs often substantially higher values in order to reward and incentivise R&D investment in rare diseases.[1] The price ratio between the top selling orphan drugs and comparable non-orphans is 8:1 according to a recent publication.[12] Thus, next to effectively "moving the needle" in addressing unmet patient needs and significantly improving quality of life[2], payers are finding that specialty, advanced and orphan therapeutics also can substantially move the needle in terms of cost. While the outlay for an individual orphan drug may be relatively modest, the cumulative impact of the rapidly increasing number of novel rare disease treatments increasingly contributes to budgetary constraints.[3] Consequently, there is an intensifying sustainability debate surrounding policies for rare diseases and orphan drugs.

In Europe, one of the main factors limiting access is no longer marketing authorisation, but the Health Technology Assessment (HTA) in individual counties.[3] While marketing authorization, for eligible products, has been harmonized with the EMA's centralized procedure, pricing, market access and HTA remain at the full discretion of the Member States. This has resulted in marked differences in the availability and utilization of transformative medicines from country to country, a matter of great concern to multiple stakeholders.[3,4]

Viewpoints, experience, resources, processes and legal frameworks differ considerably between the national HTA agencies: "if you have seen one HTA system, you have seen ONE HTA system".[5] Most importantly, there is substantial heterogeneity between HTA bodies in the methodological approach to value appraisals.[4,5,6,7] This leads to a lack in predictability and divergent outcomes of HTA evaluations and reimbursement decisions.[4,7] Given that it is not rational to commit resources to (accelerated) marketing authorisation if timely market access cannot be achieved, from the industry's perspective, HTA is a crucial success factor.[4]

The rising influence of patients and their representatives has led to a recognition that patients - and physicians - are often willing to accept greater risks and side effects from treatment of life-threatening and severely debilitating diseases in return for earlier access, especially when there are no alternative treatments available. Demands for more rapid development, approval and particularly greater access to transformative medicines have led to political pressure on HTA bodies to harmonise, better coordinate and accelerate their work and decision-making (e.g. "The EURORDIS Call on Payers to get things done").[8]

In response, a number of initiatives to reinforce EU cooperation in the area of HTA have been launched, including the European Commission's HTA Network,[9] the EMA's parallel scientific and HTA advice,[10] EUnetHTA,[7] and the "Mechanism of Coordinated Access to Orphan Drugs" (MoCA).[11] However, progress has been modest and debate on the best way forward is ongoing.[4]

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One of the key trends emerging is that European countries will club together more frequently to increase their power in price negotiations, e.g. the Benelux initiative to negotiate orphan drug purchasing.[12] While harmonizing and accelerating HTA is a part of these initiatives, their main focus lies on leveraging greater purchasing power and cost cutting. A further trend is that patients will have a key voice in HTA procedures, not only at central level during EMA/HTA parallel scientific advice meetings, but at national levels when early access is considered.[8,10]

With the increased fragmentation of treatment populations and non-conventional treatments, established drug development and regulatory paradigms, e.g. large, traditional phase 3 studies, are being increasingly challenged. Adaptive routes of development and conditional marketing authorization on the basis of less complete data with comprehensive evidence generation post-authorization will therefore become much more commonplace.[2,10,13]

Adaptive development and conditional authorization, where benefits and risks are confirmed when a medicine is already on the market, imply adaptive pricing and reimbursement models. Prices should flexibly move upwards should a drug demonstrate a better than expected benefit/risk ratio in the real world, and move downward if it fails to confirm its early promise. However, some HTA bodies have expressed scepticism regarding early value appraisals based on greater uncertainty as well as for flexible reimbursement models.[13] In Europe, this reluctance is partially explained by a lack of good experience with adaptive and conditional pricing models and outcomes- or value-based managed entry agreements, although these are innovative and increasingly used approaches.[4,13] In certain countries there is a lack of legal frameworks to implement flexible reimbursement models.[13] The comparatively greater flexibility of payers in pricing negotiations in the United States is one of the reasons access to orphan medications in the US is greater, although patient co-payments can pose significant barriers to access.[14]

All stakeholders in Europe agree, however, that progress in HTA cooperation and early market access must be made in order to ensure that patients in the EU have access to safe, effective and affordable medicines. "Collaboration is key, solutions can be found by changing the culture of interactions and building trust." [13]

In conclusion, for developers of transformative specialty and orphan medicines, value demonstration, particularly on the basis of less complete data, is an essential component of early market access strategy and evidence generation planning. This should include:

- Comprehensively documenting the burden of disease and unmet needs of patients
- Contextualising the potential benefits and value the new medicine will create as compared to existing treatments in an early value proposition strategy
- Conceptualising study designs and endpoints that are relevant and actionable for HTA as well as regulatory decision-making

Industry should seriously consider seeking early dialogues (before/during proof of concept) with multiple HTA agencies and/or joint EMA/HTA scientific advice to discuss potential adaptive development pathways and study design options, with the objective of ideally agreeing on one set of studies that will address the requirements of both regulators and HTAs. A number of initiatives are available to industry, which facilitate open and informal presubmission discussions

in a "safe harbour" approach. These include the EMA's PRIME and Adaptive Pathways[10,13] and EUnetHTA's Joint Action 3 (Strand A – Early Dialogues).[15]

About ORPHA Strategy Consulting

In rare diseases and for transformative medicines, **early access strategies, benefit/risk and value demonstrations** are often **uncharted terrain**, requiring highly specific expertise and experience.

ORPHA Strategy's principal, David Schwicker (https://www.orphastrategy.com/biography/), has industry consulting expertise spanning more than 25 years, and has gained a unique understanding of how early access programs, initiatives, and rare disease and orphan drug incentives can benefit a client's transformative medicine to **prospectively accelerate marketing authorization and market access**. To this is added a focus on **innovative development pathways** that emphasise the use of **real-world evidence**.

Thank you for your interest. To start a strategic discussion on early access, please contact:

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