Considering Commercial Success During Clinical Development: Maintaining a Global Perspective

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Although commercial success is the ultimate goal of pharmaceutical research and development (R&D), many new treatments do not meet expectations and fail to achieve broad global reimbursement after initial regulatory approval.[1,2] This causes therapies to underperform across international markets and, more importantly, limits access for patients in need. For example, only 56% of all new drugs approved by the European Medicines Agency (EMA) between March 2000 and March 2018 went on to receive a positive reimbursement recommendation by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK)—the country's central health technology assessment (HTA) body.[3]

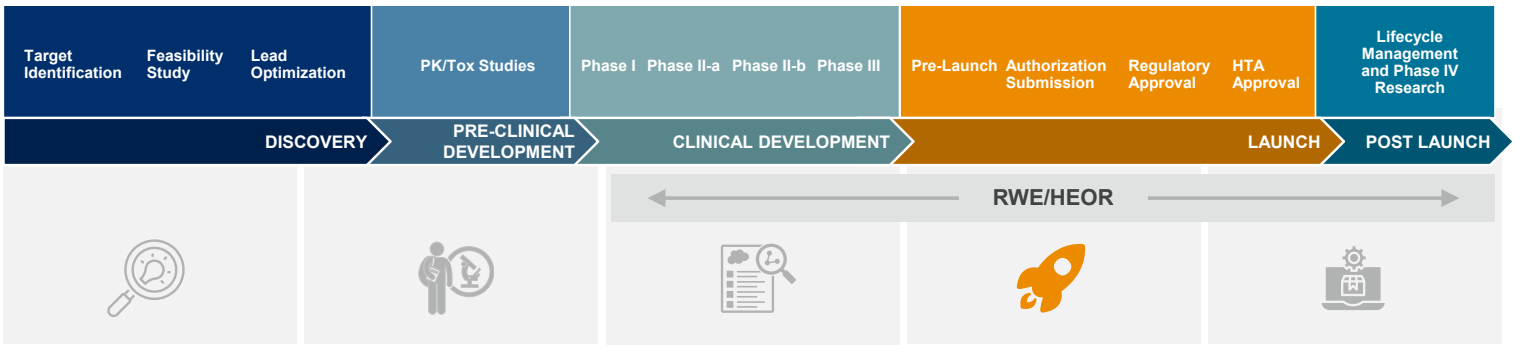
Several factors contribute to suboptimal global reimbursement, including a bias toward United States (U.S.) market characteristics and the compartmentalization of expertise within specific stages of the R&D process. As the single largest pharmaceutical market, U.S. market considerations heavily influence the focus of global pharmaceutical R&D programs despite differing market access requirements in other regions. Indeed, the differences between regional markets means a "one size fits all" approach is not feasible for achieving global commercial success. In particular, regulatory approval is generally sufficient to achieve U.S. market access, and most phase II and III clinical trials focus predominantly on obtaining the clinical safety and efficacy evidence needed to achieve regulatory approval. However, in many non-U.S. markets, new drug candidates must overcome several additional mandatory steps to gain market access, including demonstrating cost effectiveness and affordability.[4] Nevertheless, demonstrating economic benefit is becoming ever more important to supporting optimal product revenue even in the U.S..

Furthermore, there is often compartmentalization of expertise within the three main stages of the pharmaceutical R&D process: discovery research and preclinical development, clinical development, and post-approval commercialization (see Figure 1).[5] When those involved in each stage focus only on achieving progression from their stage to the next and sufficient consideration is not given to the overarching commercial objective—such as gathering the data required to support reimbursement and associated commercial success—the task of achieving this success is even more challenging.

The Value & Evidence experts at EVERSANA™ have substantial experience in establishing the evidence base required to support product value globally, which is essential for reimbursement success. Our team has supported numerous clients in demonstrating value and achieving reimbursement in global markets. For example, our team provided extensive support for the client's first-in-class biologic therapy across two indications in dermatology and rheumatology, including a thorough review of clinical and economic evidence for the product; the development of multiple global economic models and value communications; the conduct of systematic literature reviews and indirect treatment comparisons; and support for region-specific analyses, model adaptations and responses to Health Technology Assessment (HTA) queries. Our expertise has helped this client achieve global commercial success for their product, despite a crowded treatment landscape.

An important step to gaining market access in Europe and many other regions is assessment by HTA agencies. These agencies are responsible for reviewing all available clinical and economic evidence for the product and providing recommendations regarding reimbursement. Without governmental reimbursement, funding is extremely difficult, and as such, HTAs are critical for market access and represent a distinct assessment stage after approval by the competent authority.[4] It is well recognized that HTA agencies

FIGURE 1: Overview of Decision Points and Development Stages of Health Technology Research and Development



require evidence regarding the cost effectiveness and relative clinical efficacy of a new treatment, the most important of which is generated through clinical trials. Where insufficient data have been generated by clinical trials, evidence can be supported by activities including systematic literature reviews (SLRs), indirect treatment comparisons (ITCs) and economic modeling activities.[4]

For example, a recent study of reimbursement decisions for 33 drugs that received regulatory approval and were evaluated by HTA bodies between 1995 and 2018 revealed that HTA bodies raised uncertainties regarding the relative effectiveness, evaluated endpoints and longterm outcomes substantially more than regulators. This highlights the need for stakeholders involved in the design of clinical trials to consider inclusion of endpoints and comparators relevant to HTAs—including outcomes that may assist in determination of a drug's cost effectiveness and budget impact—as early as phase II in clinical development.[4, 6] Importantly, this should occur in addition to and in collaboration with the needs of regulators.[1, 7] Furthermore, it is important to note that collection of economic data, although not strictly necessary for market access in the U.S., is still valuable to maximize performance in the U.S. market.

A key question based on this information is how pharmaceutical, biotechnology and medical device companies should ensure HTA requirements are considered during product development. It is critical to engage HTA agencies as early as possible and to reflect their feedback in clinical development plans. Opportunities should be sought to obtain early insight on evidence needs (including appropriate comparator and endpoint selection), which may increase the likelihood of reimbursement success at product launch.[1] EVERSANA's Value & Evidence experts leverage our extensive knowledge of global HTA requirements and our history of supporting successful global reimbursement initiatives to inform such considerations early in the development process, providing our clients with the best chances of achieving commercial success for their products.

One approach to collecting data on product value during clinical trials is through the use of patientreported outcomes (PROs). PROs that measure health-related quality of life (HRQoL) can support important value-based endpoints that help to address several aspects of payer needs and HTA requirements while also improving reporting of the patient experience in clinical trials. HRQoL data are commonly considered in value assessment frameworks, which provide tools to assist payers with reimbursement decisions and include recommendations on resource allocation to achieve the best patient outcomes.[8,9-14] National HTA agencies in Canada and Europe also emphasize the importance of HRQoL data in clinical trials. For example, the pan-Canadian Oncology Drug Review (pCODR) deliberative framework includes HRQoL as a component of the effectiveness assessment.[15]

Despite their suitability in obtaining value-based data, PROs remain consistently underreported in clinical trials.[12, 16] For example, although HTA agencies from six European countries all consider HRQoL a relevant endpoint in clinical trials, only 54% of relative effectiveness assessments for oncology drugs approved by the EMA between 2011 and 2013 had trial data for HRQoL.[17] Beyond insufficient priority being placed on obtaining value data through inclusion of appropriate PROs in clinical studies, it is likely there is concern that including these endpoints would be prohibitively expensive or, worse, undermine regulatory approval. This "risk aversion" among clinical development specialists is understandable, but it is important to note that in the study referenced above, the PRO results impacted the recommendation 74% of the time and, within that, had a negative impact on only 7% of recommendations.[17] These findings support the notion that there is limited downside to including PROs as trial outcomes from the HTA perspective.

Beyond HRQoL, examples of additional endpoints that are important for determination of value in HTAs and should be implemented more broadly into clinical trials include measurements of patient productivity and activities of daily living (and associated impact on caregivers); comorbidities that may be assessable through PRO measures (e.g., anxiety and depression); and healthcare resource utilization outcomes such as hospitalizations, surgeries or clinic visits required for supportive treatment administration.[8] Each of these endpoints helps to determine potential cost offsets that may require incorporation into pharmacoeconomic analyses used in HTAs.

Nevertheless, many of the endpoints of interest discussed above can require large sample sizes, long follow-up periods or both to obtain the data necessary to interpret clinically meaningful and/or statistically significant differences between study arms. Additional patients, which may require additional sites, and extended timelines are major clinical trial cost drivers. Furthermore, collection of these data may not be possible for trials of rare diseases and conditions

with poor prognoses, for which high enrollment and longitudinal observation periods are not feasible. In addition, given that only a limited number of study arms can reasonably be included in each trial to maintain power in planned statistical analyses and that comparators differ greatly between regions, it is often impossible to include every comparator of interest to meet the needs of all regional HTA bodies.

With these limitations in mind, it is likely that following early engagement with HTAs, inclusion of obtaining these key additional data is considered during protocol design. For those cases when collection of all data required by HTAs is not possible through clinical trials, evidence synthesis activities—including real-world evidence (RWE) studies leveraging data from established databases and registries, generation of synthetic control arms, and comparative effectiveness studies such as ITCs and network meta-analyses (NMAs)—provide important opportunities to help fill evidence gaps. The data generated by these activities can also help to support economic model development, increasing the opportunity to consider relative effectiveness data for multiple comparators and providing additional flexibility for economic evaluations across regions.

Working with Health Economics and Outcomes Research (HEOR) consultants—such as EVERSANA's Value & Evidence experts—early in clinical development can help to ensure appropriate trial design to meet the evidence requirements of HTA agencies and to develop a robust evidence generation plan. The earlier these activities are planned, designed and executed, the more opportunity there is for subsequent analyses to continue building an evidence base that provides a manufacturer with the best chance of commercial success for its new drug at the time of launch.

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