Avoid Last Minute Rush—Planning Ahead for Successful Global Market Access

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In today's healthcare environment, there is increasing pressure to demonstrate evidence of product value, whether in terms of cost, effectiveness, or both. Both public and private healthcare payers increasingly require evidence of effectiveness to cover or reimburse for the use of drugs and medical devices. Even drugs and devices that have regulatory approval and coverage in certain indications face restrictions for indications in which evidence is not deemed sufficiently robust. To meet this increasing demand, it is crucial to begin planning an evidence strategy early to maximize the chance of success for global market access. This article will focus on three things: 1) why it is important to plan early, 2) what should be considered in this planning, and 3) how to approach the planning process.

Each organization certainly has its own definition of market access planning, but for the sake of this article, it is considered a component of the overall commercial plan for a product, including regulatory strategy, clinical development planning, and communication strategy addressed from a global perspective and not focused on local or national level activities.

SETTING THE STAGE—A CASE STUDY EXAMPLE

Challenge

Evidera was approached by a client with a compound in late Phase 2 clinical development; there was, however, no clear picture of where the product would fit in the market or what type of support was needed for market access.

Approach

The client provided Evidera with a number of materials including clinical results from Phase 2, the target product profile, and key opinion leader research. We conducted supplemental targeted

research, including looking at current and future competitors, reviewing health technology assessments for insights on evidence requirements and reviewing the clinical guidelines to look at positioning of existing products.

Results

An assessment was made of the product's potential contribution in satisfying some of the unmet need in the disease area. A document was developed outlining additional activities needed (e.g., literature review, payer research) and associated timelines. Using this document, the company could then create project priorities with transparent rationale for their internal colleagues and commission the needed work confident in the knowledge that these pieces of work fit together sensibly and coherently in a broader strategy for market access for the product.

Lessons learned

1. Thinking and planning ahead led to understanding the context of the product in the marketplace and the evidence gaps where additional activities were needed.
2. There is value in looking at all the evidence needs at one time in order to prioritize next steps wisely and avoid moving forward with near-term activities without considering the full breadth of activities needed to build the strongest evidence value story.
3. Bringing together a diverse group of colleagues with varying roles and views across the company strengthens the team's understanding that access activities are integral to the clinical development and overall commercial strategies.

WHY PLAN EARLY?

Everyone is always told to plan ahead, but what if that does not happen? Can we get away from doing only part of the planning? And how early does that really have to begin? Often in early phases of product development, budgets and people resources are limited; allocating time and energy too early is questioned when budget allocation for projects has a low probability for approval. Or the early phase product planning is under the responsibility of another department, so engagement around market access issues is delayed until the product responsibility is transferred.

We would challenge, however, that expectations of all facets of decision makers should be taken into consideration early in the product development cycle. However, internal stakeholders may have conflicting goals. Ideally, companies want to get a product label that is as broad as possible, so clinical trials and dossiers for regulatory bodies are designed to that end. Payer and reimbursement authorities, however, are asking more pointed questions.

- Who is the target audience for this product?
- Where does this product fit in the marketplace along with generics, biosimilars, etc.?
- Are there sub-populations where the product is the optimal treatment option?

Payers may prefer offering favourable reimbursement for a product that brings innovation to a small subset of patients rather than to a product that provides no additional innovation in the total disease population. There is a growing desire to provide products to niche patient groups or settings in which they are most effective. For example, a major aspiration of the U.S. comparative effectiveness research (CER) effort is to determine "what works for whom under which circumstances?" Manufacturers must consider identifying a target population (ideally, one with high unmet need) in their evidence generation planning to support the value story, without overly restricting their product. Each stakeholder has their preference in this area. For example, the U.S.

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Food and Drug Administration (FDA) wants robust results without post hoc analyses, such as covariate adjustment, sub-setting, or reduced data sets, while payers may be more amenable to either post hoc or evidence development from observational studies to understand the target population. Payers have the ability to restrict usage, so they may decide on the treatment line in which the product can be used. Lastly, there is increasing importance on providing long-term or real-world data to confirm what was observed in clinical trials. The inclusion and timing of these study types must be assessed internally based on decision maker requirements and specific characteristics of the product (e.g., if the features of the product support better adherence, this is something that will need to be studied in a real-world setting).

Consequences exist when some of these issues are not considered early in the development process. Payers may reject or restrict products if the evidence requirements are not fulfilled and submissions do not contain the appropriate data, such as weak comparative clinical data, inappropriate comparators in clinical trials or health

economic modeling, or lack of agreement of economic modeling methodology or model results. As a result, products may be restricted to a specific subgroup of patients instead of the broader use the company would like. Additionally, risk-sharing schemes or value-based pricing may be required to gain access for high-cost products, where manufacturers pay for patients who fail to respond to treatment and payers only pay for those who positively respond to treatment. As an illustration of these consequences, the National Institute for Health and Care Excellence (NICE) performed 207 appraisals over a 10-year period with 409 recommendations for action.[1] Of these, NICE rejected 46 products due to lack of data—three of which are highlighted below.

- An adjuvant treatment of gastrointestinal stromal tumours—The evidence base was too undeveloped to draw conclusions about key aspects of clinical effectiveness. Two years later, newer data were available and NICE indicated they were willing to re-evaluate the evidence, but there was a two year gap because the evidence was not available for the initial submission and review.
- A treatment for metastatic colorectal cancer—The economic evidence was considered weak because disutility due to adverse events was not included; unit cost estimates for the comparator were unclear; and costs of patient access scheme were underestimated. Additional information was provided two years later that resulted in the treatment now being used as second-line treatment, but again, there was a two year delay because of insufficient evidence in the original submission.
- A treatment for locally advanced or metastatic breast cancer as a follow-on product after an aromatase inhibitor—The evidence presented was not aligned with the scope of the submission—the benefit of the drug was only for patients whose last therapy was an anti-oestrogen and not for patients whose last therapy was an aromatase inhibitor. The therapy was not recommended as an alternative to aromatase inhibitors and is still listed as a non-preferred product on NICE's website.

WHAT SHOULD BE CONSIDERED?

In planning your evidence strategy, there are several things to consider. First, what can be used for regulatory approval and what is needed for reimbursement authorities? When presenting to a regulatory authority, the main consideration is a benefit/risk assessment, i.e., is the product safe and is it effective in a controlled environment? Conversely, when communicating with a reimbursement audience, the focus should be on the relative efficacy or the relative effectiveness, i.e., compared to the treatment options that are available in the marketplace, what is the additional benefit of this new medicine?

Next to consider is internal and external validation of the evidence.

- Internal validity is the focus of a regulatory submission, so a well-controlled clinical trial where you can control all the meaningful factors and utilize randomization as a component.
- External validity focuses on real-world effectiveness and the impact on the healthcare system.

The type of data follows from this, moving from the clinical trial to observational data and modeling. Preferred endpoints for a regulatory submission focus on surrogates and hard endpoints, whereas a reimbursement authority is looking not only at the target endpoint, but also for quality of life and patient-reported outcomes.

Lastly, evidence requirements vary greatly from country to country, where some countries only require clinical data (either efficacy or effectiveness data) and others request both clinical and cost-effectiveness data. Additionally, there are implicit and explicit costs-per-quality-adjusted life year (QALY) thresholds for individual countries, and, in some circumstances, those vary depending on the class of medicine. This last point shows that once regulatory approval is received, it is important to think about the priority countries and what the evidence requirements are for those given countries.

NOW WHAT? HOW TO APPROACH THE PLANNING PROCESS

In planning a study strategy, it is important to think of this as a series of investment questions and decisions.

1. *If investment is made earlier in the process, will it change the uptake and the revenue that is generated for the molecule?*

Investment begins in research and then continues at varying levels along every stage of the process, including development, registration and commercialization. Early on, the investment is relatively low, but that investment expands at the point of registration. At this point, there are many considerations, including thought leader endorsement, formulary positioning, clinical guidelines, treatment pathways, etc., but the major three considerations are filing the first registration, targeting the first launch, and developing the dossiers for pricing and reimbursement authorities.

Typically the thinking is that the Phase 3 clinical trial program has a three to five year timeframe until the data are reported out and available. In some instances, the additional evidence, beyond the clinical trial results, such as an economic model, is not commissioned

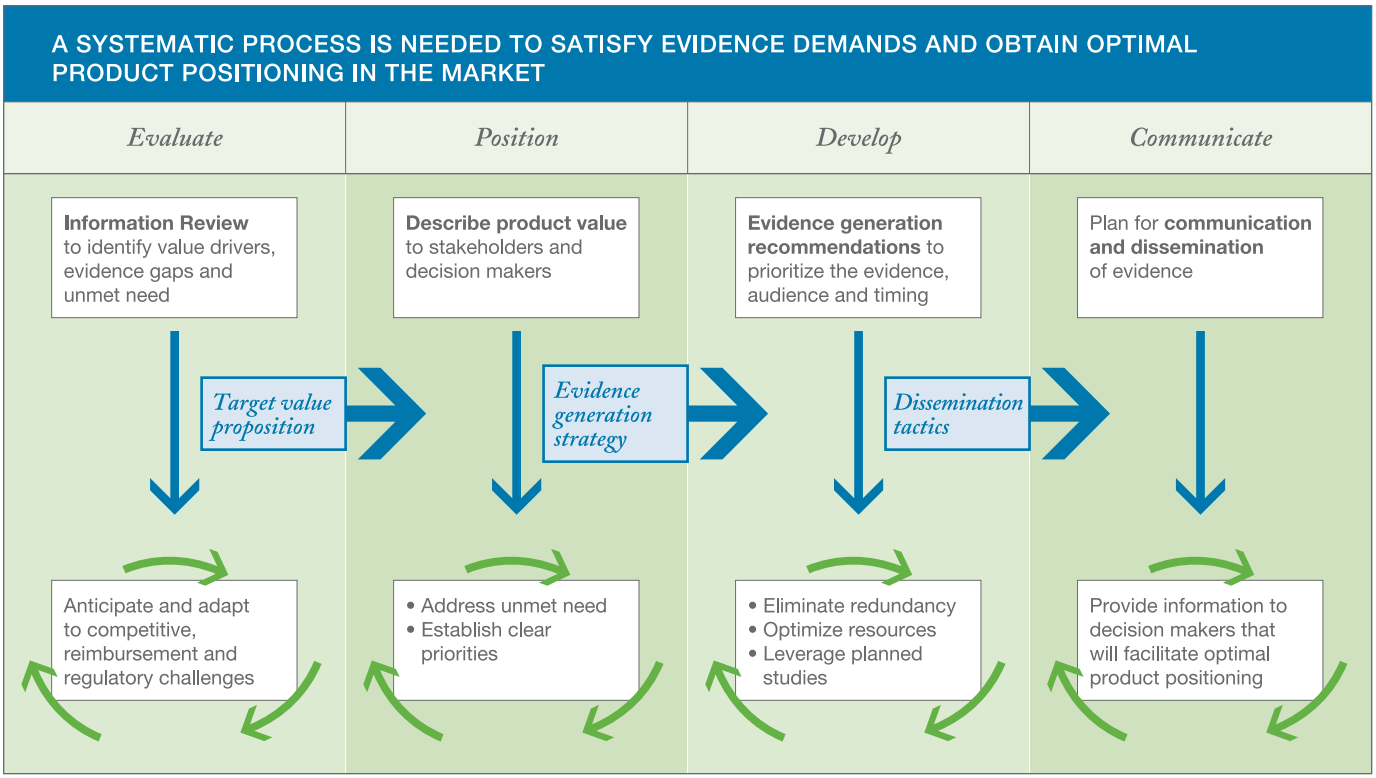

figure 1

until Phase 3 is nearly complete. But in reality, the economic modeling should begin concurrent to Phase 3, utilizing the Phase 2 results to inform product pricing through estimation of the product cost-effectiveness ratio. This allows the organization to consider possible strategies to optimize market access. This might be through evidence generation to better document the economic impact or to re-evaluate the target population.

The end goal for any product planning is to grow revenue, so by planning and investing earlier in the process, revenue and uptake should come sooner and the market share would be larger than would be expected if that parallel planning did not occur. Referring to one of the previous NICE examples, there was a two-year window that may have been significantly shortened had there been earlier thought for those particular products.

2. *Who needs to be involved in strategy discussions? What are the key activities that need to be planned and how are they aligned with the current decision-making process?*

Internal decisions can occur early, typically around Proof of Concept (PoC) and further in development, at entry into the Phase 3 program; at each of these time points the strategy is updated as commitment to launch the new product is reviewed. This is the time that market access and reimbursement strategy should also be considered. For example, at the same time that external clinical experts are being included in the process, advice should be sought from payers and payer representatives on the gaps that exist in the evidence and how to plan activities to meet their needs. Aligning your value development strategy with internal stakeholders, such as commercial, medical affairs, market access, etc., at key decision points and activities is essential to ensure appropriate planning and strategy across all areas of the company.

Beyond the global strategy, the process also needs to be considered at the study level. One might consider the following:

- When designing Phase 3 trials, are the right comparators available and being used?
- Are endpoints being considered which are needed to populate an economic model or begin to link to the real-world or clinical practice data?
- If there is a particular lab value being looked at in the study as a surrogate efficacy endpoint, what is known about that lab value in clinical practice, and can changes in that parameter be linked to the economic impact for the patient?

3. *How is the plan executed within the organization?*

A systematic process is needed to satisfy evidence demands and obtain optimal product positioning in the market. As previously mentioned, each company approaches this differently, so the first step is assessing a company's current process to see where adjustments may need to be made for optimal evidence generation and planning.

In developing a full evidence development plan, or value demonstration strategy the first step is to do a complete information review to identify where evidence gaps exist and where there are opportunities for the product to address unmet need. This helps to establish the value proposition for the product. Once this is known, an evidence generation strategy can be developed that specifies what evidence is crucial to support the product and what approaches or studies are needed to develop the value story for all stakeholders in a coherent and cost-efficient manner. Lastly, the right communication plan must be established to disseminate the evidence in the right way to each stakeholder *(see Figure 1)*.

Evidera has collaborated with clients where the timing of the preparation of value demonstration strategy (VDS) was not ideal. In a number of circumstances, this resulted in siloed activities, duplicity in effort, and inefficient use of company resources. The following case describes an effective, early approach to creating a VDS.

SUCCESSFUL CASE STUDY

Challenge

A large global pharmaceutical company had a new compound in Phase 2 with a novel mode of action and expected to be first in a new class of drugs. The treatment would offer significant benefits to patients and providers, but would face considerable challenges from payers and health technology assessment (HTA) agencies. The client needed a health economics and outcomes research (HEOR) strategy to meet payer and HTA agency evidence needs once Phase 2 data was available.

Approach

The process described above was used to outline the needs. A targeted literature review was conducted to specifically look at health technology assessments (HTAs) that had been done in the disease area and identify evidence gaps. Those gaps were then prioritized in light of the compound's target product profile based on Phase 2a results.

Results

A priority list of projects was identified, along with costs and proposed timelines, to generate and communicate the evidence required for payers and HTA agencies in Europe. Simultaneously, the company sought advice from an HTA agency and was then able to compare our recommendations against those of the HTA agency, which were found to be in alignment. This gave the company confidence in the health economics and outcomes research (HEOR) strategy proposed and they were able to move forward with the planning with the knowledge that the strategy was aligned with the overall commercial strategy and would also address likely questions and challenges that payers and HTA agencies would pose at the time of launch. Local affiliate companies were also able to align with the company's R&D division's approach, capturing efficiencies across Europe in the preparation for launch.

With continually growing requirements from different decision makers, the need for credible evidence and strong value stories geared towards the right audiences at the right time also grows. Add that to the challenge of constrained company budgets and it becomes clear that the strategy needs to be developed as early as possible to ensure the right evidence is generated in the most cost-effective manner. While companies are still hesitant at times to make large investments in new treatments early in the development stage, there is increasing awareness that early investment can be more cost-effective in the long run. Yes, things have changed over the years, and if this evolution toward more rigorous evidence requirements is ignored, there can be consequences—consequences which impact the trajectory of product uptake and the size of the peak revenue.

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References

[1] National Institute for Health and Clinical Excellence (NICE), Technology Assessment (TA) Decision Table, 2010. Available at: http://www.nice.org.uk/guidance/ta/published/index.jsp?p=off. Accessed Apr 23, 2014.