Early Scientific Advice from Regulators and HTA: An Industry Perspective

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KEY POINTS . . .

Scientific advice has been very helpful for industry.

Companies often have more than one product in their strategic focus areas. They will need less product specific advice and more disease area and technology guidance.

As products are now reaching the market, for which scientific advice was sought, we will need to start more formal evaluation of the process and its outcomes.

An Industry Perspective

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Introduction

From an industry perspective, scientific advice provided by HTA agencies and payers serves several purposes: Provide an HTA perspective on the evidence program, achieve internal alignment on the design of the phase 3 development program and proactively engage with key stakeholders at an early stage of product development. Generally, regulatory specialists in the industry have always had very clear guidance from regulatory agencies which has resulted in a focus on clinical development programs on regulatory requirements. For those representing a health technology assessment (HTA) and payer perspective in the company, it is important to have the same alignment with HTA agencies and payers, to ensure clear prioritization of activities and endpoints associated with the Phase III program.

Scientific advice is of particular importance in cases such as the investigation of novel mechanisms of actions in new or poorly understood diseases in which there is little experience and guidance on endpoints, patient populations or trial designs. In such areas, there are many open scientific questions and development of a common understanding between industry, HTA and regulators of the best solutions within the Phase III program is very important. There was a time when industry and payers did not meet frequently, except for the actual price negotiation. In the past 10 years, however, more willingness on all sides to engage throughout the development process and create transparency concerning expectations has been seen.

Expectations from Industry

The industry expectations of the scientific advice process are centered around an aligned trial design; specifically on comparators, endpoints, patient inclusion criteria and duration of trials. Industry wants to achieve this alignment between the manufacturer and the HTA agency and potentially across different HTA agencies and regulators. Industry also expects that the HTA agencies better understand the difficult tradeoffs and limitations of phase III clinical development.

At the point in time when the scientific advice is sought, the available evidence is limited to preclinical and early human data, typically from Phase II trials. The design of phase III programs is based on hypotheses generated through these early trials, and is optimized to characterize benefit and risks in the most efficient way by exposing the minimum number of patients to an investigational compound. This may not always be aligned with HTA and payers that want longer term observation in heterogeneous patient populations against sometimes multiple active comparators. While scientific advice is not legally binding, there is an expectation that by following the advice industry receive some endorsement from HTA and payers for the design of the evidence generation programs. Several questions that HTA may have at the end of the trial are often not obvious early on. In hindsight, it sometimes appears as though certain critical questions were avoided, but the fact is that at the outset, not all requirements can be anticipated.

Initial Concerns

Regarding the scientific advice process,

Key Insights – An Internal Industry Perspective

- Advice has always been considered very helpful
- Early advice has become part of "standard operating procedure"
- Timing is difficult – always too early until it's too late
- Where phase III program has been locked, advice can still help to fine-tune statistical analysis plan and design of phase IIIb/IV studies
- Individual HTA advice is more focused on technical aspects, joined/parallel HTA/regulator advice is more focused on topline issues and alignment
- Increased the quality of advisory boards
- Increased the recognition of internal expertise
- Few products have made it to the market – too early to assess "ultimate benefit"
- Even where products have failed, the advice was useful

Key Insights – An Industry view on Regulators/HTA

- A new market place for providing advice – throughout the product lifecycle
- Advice usually very constructive – willing to consider alternative designs
- Meetings have become more of a dialogue
- Scheduling is increasingly difficult
- HTA and regulators have been grateful when we provided feedback

industry has initially voiced many concerns. The most prevalent concern was "be careful what you ask for." Is it better to plead ignorance and say you did not know what HTA and payers expected, or to go out and ask for this advice and accept it, even if it results in more complex and lengthy clinical development programs? Everybody by now has agreed that the first is not really an option. Another concern was whether early engagement will "sanction," encourage or accelerate additional evidence requests from regulators. These concerns are valid as clinical development programs increase in both complexity and cost. Building on this, an additional concern is whether the process of preparing for and receiving advice will be cost-effective. It has been shown that many of the HTA advisors are interested in encouraging more efficient development programs. However, preparation for scientific advice within industry takes teams of significant size about six to eight months, often in addition to the time required to prepare for scientific advice from regulators.

Key Insights

From an internal industry perspective, there are many key insights concerning the scientific advice process. First of which is that advice meetings are always considered very helpful. Because of this, the early advice has become part of the "standard operating procedure." It is important to keep in mind, however, that scientific advice through face to face meetings with the agencies is not the only way of validating the Phase III programs. Advisory boards with experts familiar with regulator and HTA requirements are still used. In addition we can call on the expertise within the companies themselves, in particular from colleagues in affiliates that are in frequent interactions with HTA and payers. With this scientific advice process the payers can now directly offer advice, which has served to increase the quality of the advisory boards by helping to better understand the development process. The process has also helped to increase the recognition of the internal expertise at the country level.

Another insight is that finding the appropriate time to get the advice may be difficult. It is always too early until it is too late. It is considered too early when you do not have any Phase II data, but once you have the data everything goes very fast. In cases where the Phase III program has been locked, getting the advice is still very useful. The scientific advice can help to fine-tune statistical analysis plans and the design of the Phase IIIb/IV plans. There are indirect treatment comparisons and other methods for which you can prepare for when the Phase III program is locked. Individual HTA advice with specific agencies is more focused on technical aspects such as endpoints and requirements to conduct valid treatment comparisons as well as economic evaluations surrounding it. On the other hand, joint/parallel HTA/regulator advice is more focused on topline issues, alignment, and how every participant's expectations can be met. Looking at the advice process from a product standpoint, it is too early to assess the "ultimate benefit" as only a few products have made it to market as of yet. However, it is important to recognize that even for the products that failed, and probably around 30-40% of the products fail during the development program, the advice is considered useful because the information provided during the process can be used by the company at a later date.

From an industry perspective on regulators/HTA, this process has created a new marketplace for providing advice throughout the product lifecycle. Many HTA agencies now offer this and industry can choose from which to seek advice. Additionally, the advice that is provided is usually very constructive. There was an initial concern that the HTA Agencies would provide advice that was in contradiction to those agreed between industry and regulators, but there has been a willingness to consider alternative designs. The actual advice meetings have progressed to become more of a dialogue as compared to the very formal and restricted meetings at the onset. Scheduling continues to be increasingly difficult. For example, NICE provides very good advice, but the industry has to request scientific advice meetings approximately nine months prior to initiating the actual process. This is difficult as time slots must be booked in advance without the knowledge of whether or not they will be at the correct program stage at that time. Lastly, HTA and regulators have appeared to be particularly grateful when industry provided feedback on how their advice was used in the final design of the development program.

Critical Success Factors and Outlook

Some of the most critical factors for success with this scientific advice process are internal preparation, seniority and the experience of meeting participants, adequate resources, and follow up after the meeting.

Experience is not only important on the industry side but also within the regulators so that the underlying science could be explained and not limited by the participant's respective backgrounds. The resources provided by the national HTA agencies should be able to support national as well as multinational scientific advice processes. In addition, follow-up after the meeting, particularly internal meetings, is important because the information received needs to be organized so that it can be appropriately acted upon.

The industry opinion is that every pharmaceutical company has a finite number of strategic disease areas in which products are explored with payers. It is assumed that the actual number of product-specific advices that are required by the large pharmaceutical companies may decrease over time. This decrease is due to fact that future products may be applied to disease areas in which advice has already received. Unless the scientific advice is strongly recommended by law, the companies will carefully consider the added value of the advice. This advice was needed years ago to convince industry internal organizations about the evidence needs of payers, but increasingly, industry should be at the point where they understand the requests that are placed before them. As the products, for which scientific advice was sought, are now reaching the market, a more formal evaluation of the advice process, its benefits, and its outcomes is due. This broad evaluation is not something to be done by one company, but something that should be accomplished on a larger scale with cooperation between different companies and agencies. ■