To SPA or Not to SPA: That is the Question

Understanding Special Protocol Assessments

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Introduction

The ***Guidance for Industry: Special Protocol Assessment (SPA)*** was issued in May of 2002 with the express purpose of allowing FDA to provide input into the design of phase 3 clinical protocols, animal carcinogenicity, and product stability, thereby giving FDA the opportunity to come to agreement with the product sponsor on the scientific and regulatory requirements of the study prior to its initiation. This paper will limit itself to the consideration of phase 3 clinical protocols and will not deal specifically with the process of requesting and executing an SPA. Rather, we will provide strategic recommendations for the effective use of SPAs in product development and explain how this SPA FDA guidance is best used in light of the recommendation in the ***Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants*** (May 2017) for each product sponsor to conduct an end-of-phase-2 (EOP2) meeting. Both guidances were developed to encourage product sponsors to interact with the FDA prior to initiating their phase 3 program, but the timing and the strategy for each company may differ depending on the specifics of their development program, resulting in a product sponsor's choosing to participate in both FDA guidance processes or only one.

SPA Experience

Since the issuance of the SPA Guidance by FDA in 2002, the pharmaceutical industry has been regaled with scintillating stories of accelerated development due to the institution of this process. Unfortunately, there have been at least as many stories recounting the SPA process as something tantamount to orbiting the sun in terms of time invested.

The reasons for lack of success can be multifactorial but typically result from one or more of the following problems:

1. Failure to provide FDA with an adequate scientific and regulatory clinical protocol and accompanying statistical analysis plan in the SPA request submission

2. Failure to provide FDA with clear and concise questions regarding the clinical protocol in the SPA request submission
3. Failure to negotiate with FDA on a scientific and regulatory basis regarding the clinical protocol design

Let's take each of these problems in turn and reflect on solutions that would allow the product sponsors to have greater success in the future with an SPA submission.

Design of a phase 3 protocol is one of the most difficult activities in any product development program and consequently deserves the time and resources necessary for it to be done thoroughly. While nothing is that intellectually daunting, the sheer complexity of the exercise makes it a significant challenge. Designing a scientifically and regulatorily acceptable adequate and well-controlled phase 3 study is impossible if the requisite questions regarding the investigational product development have not been answered in a phase 2 program (e.g., minimum effective dosage, appropriate subject population, a clear and quantifiable definition of success for the primary objective). The most important element in any phase 3 protocol design is ensuring the correct primary clinical endpoint is identified and vetted clinically, scientifically, statistically, and regulatorily. Falling short on any one of these fronts will lead to failure.

FDA is best not viewed as a product development consultant, but rather as a confirmatory body. If sufficient due diligence is done prior to approaching FDA, the chances of success are much higher. The clinical endpoints must be rock solid if you anticipate a successful SPA. If not, alternative approaches such as an end of phase 2 (EOP2) meeting or a Type C meeting are recommended to resolve these design or analysis uncertainties if all efforts to explain these issues outside the FDA have met with failure. While FDA commits to conducting a Type A meeting if the SPA response is not sufficient, the most efficient SPA processes come to agreement without the need for a meeting.

The second issue of failure to provide FDA with clear and concise questions is a common problem facing the industry because there are relatively few opportunities to interact with FDA and consequently the ability to hone these elucidative skills are not frequently available among a company's employees. Moreover, some people who do have regular interaction with FDA often underestimate the importance of the questions to the success of the SPA. We believe that high level question(s) should be thoughtfully crafted and vetted through whatever review and consultation sources are obtainable prior to approaching FDA. The ideal SPA process is one in which the sponsor has performed sufficient due diligence to create a fully vetted protocol and statistical analysis plan that are presented with just a single question for FDA: "Does the agency agree that the protocol design will potentially result in data required for FDA review for marketing approval for the proposed indication." If FDA does not agree with this statement they will most assuredly provide you input to address all existing issues.

A third problem that occurs far more often than expected are product sponsors submitting an SPA while consciously or subconsciously never intending to negotiate with FDA on sound scientific grounds. Monetary constraints, either real or imagined, prevent the company from listening to the advice that FDA is providing with an open scientific mind. The product sponsor, for example, enters the SPA negotiation with a predetermined upper limit on the size of their Phase 3 study regardless of the scientific validity of the design. If the sponsor is unable or unwilling to compromise, there is never an opportunity for FDA and the product sponsor to negotiate an agreed upon protocol design during the SPA process. Obviously, this can lead to protracted discussions of limited value.

Optimal use of the SPA

In our experience, the SPA is a vehicle best used to expedite development of programs that are accelerated relative to traditional development plans. FDA often lacks historical knowledge regarding a product development program that lands on their desk suddenly from outside the US (OUS) or from a company with a creative new formulation intent on filing an NDA via the 505(b)(2) approval route. This contrasts with the historical knowledge FDA would understand for a new medical entity developed collaboratively by the product sponsor from the Pre-IND stage. These OUS or 505(b)(2) programs tend to conduct phase 3 early in their US development program and consequently getting FDA to weigh in on the design of their phase 3 clinical protocols sometimes needs to be done in parallel with other approval rate-limiting activities (e.g., Chemistry, Manufacturing, and Controls [CMC] activities).

One must be cognizant of the requirement for FDA to have some knowledge of the development program prior to the submission of an SPA in these instances. This can oftentimes be accommodated by requesting a (Pre-IND/EOP2) Type B meeting if you have questions regarding other disciplinary elements of your development program prior to the initiation of your program in the US. If the Pre-IND/EOP2 meeting discussion finalizes the design of your phase 3 studies, this can be followed by the submission of your agreed-upon study design in the IND application itself. If your program requires a safety or clinical pharmacology study to open the IND, the SPA may be used effectively to finalize the design and analysis plan of the phase 3 studies in parallel with the conduct of the phase 1 studies.

Alternatives to the SPA

One alternative to filing an SPA when input on a phase 3 protocol design and proposed analysis is desired is simply to submit a full protocol(s) to the agency as an appendix to your EOP2 meeting package. This contrasts with the Pre-IND or Type C meeting which cannot substitute for an SPA but is typically used to gather information from FDA that you have been unable to obtain from industry experts. You can phrase the questions in your EOP2 meeting request letter and briefing package to ask whether or not the protocol(s), if conducted successfully, will yield the data required to support the desired indication language on your proposed package insert. Many companies tend to ask specific questions about different aspects of the design and the analyses when a protocol is submitted as part of a meeting package. In reality, most of these design and analysis questions can be answered by non-FDA discipline experts and what is actually desired from FDA is concordance with the ability of the study to eventually support the label claim. If FDA disagrees with any element of the protocol design or the analyses, they will be sure to tell you!

If multi-disciplinary questions exist for the product, it may be useful to divide your EOP2 interaction with the FDA into two meetings; for example, one meeting to focus on the marketing application requirements for the preclinical and CMC activities and a second focused entirely on phase 3 protocol design and analysis. In this manner, sufficient time is allotted for all disciplines in the one hour provided for such meetings.

Conclusions

Use of the SPA process can be a valuable approach to expediting product development in certain cases, but it is not recommended for all development programs. Careful selection of the use of formal meetings with FDA to gather needed development information should be conducted prior to the eventual SPA process. The SPA process should be focused on submitting a thoroughly vetted clinical protocol and statistical analysis plan that are designed to provide FDA with a clear picture of how the results from successful study conduct will support the label claim for the desired indication; anything less than that is wasting both the company's and the FDA's time.

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Dr. Shoemaker has more than 25 years of experience in research and pharmaceutical development. He has served as a Program Leader or Advisor for multi-disciplinary program teams and has been involved with products at all stages of the development process. Dr. Shoemaker has managed the regulatory strategy for programs involving multiple therapeutic areas, including hematology, oncology, cardiology, pulmonology, infectious diseases, genetic enzyme deficiencies, antitoxins, and anti-bioterrorism agents. He has extensive experience in the preparation and filing of all types of regulatory submissions including primary responsibility for four BLAs and three NDAs. He has managed or contributed to more than two dozen NDAs, BLAs, and MAAs. Dr. Shoemaker has moderated dozens of regulatory authority meetings for all stages of development. His primary areas of expertise include clinical study design and regulatory strategy for development of novel drug and biological products.