



by Neil Canavan

It's been proposed that the innovation of language was driven by the innate need to complain. This concept has come full circle now that many of today's complaints are related to language itself, such as when two parties try to accurately recall a conversation, with the result being a clash between what was really said, and what was actually meant, thereby causing strained relations. To address this problem within the context of the pharmaceutical industry, the special protocol assessment (SPA) became a critical component of the Prescription Drug User Fee Act (PDUFA) more than two decades ago.

Thomas Reynolds, MD, PhD, Chief Medical Officer for Seattle Genetics, explains: "The SPA evolved from situations where there would be meetings between the FDA and a company and things would be agreed upon, but when the company went to do the filing for its drug, the FDA would come back and say, well, we never agreed to that." Before the advent of the SPA there was no mechanism of documented consensus, and now 20 years later the question to ask is, does the SPA work?

If You Ask, You Will Receive

"Initially, the FDA did not like the SPA process very much at all," says Reynolds, "they didn't want to get pinned down. Now, it's gone in completely the other direction." Cooperation between companies and the FDA is excellent, and questions about trial designs and other protocols are more than welcome.

Seattle Genetics is a recent witness to this largess, having received an SPA for their investigational compound, SGN-35 [brentuximab vedotin]. In February '09, the company initiated a pivotal trial of SGN-35 for relapsed or refractory Hodgkin's lymphoma under an SPA. More recently, they announced a Phase 2 trial in relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) as well as a Phase 1 clinical trial evaluating weekly dosing of SGN-35 for CD30-positive hematologic malignancies.

As evidence of their encouragement, Reynolds says that it was the agency that requested the SPA after

Seattle Genetics expressed an interest in an accelerated approval. "The response rates we were seeing [with SGN-35] were quite high—over 50%—that's extraordinary in a population that's failed transplant and multiple lines of therapy," he said.

Therefore, Reynolds went to the FDA to discuss using response rates as an endpoint. "We told them we thought this would be a great way to balance collecting good data, with a high likelihood of clinical benefit, while at the same time getting the drug out to the market much sooner than if we were going to do an overall survival study, or progression-free survival." According to him, that's when the agency formally requested they submit the study under an SPA.

"We got a lot of very specific feedback about what the FDA is expecting, and what we're to give them at the end of the study," says Reynolds. The assessed protocol included methods for CD30 expression; requirements for the handling of biopsies; and particulars for patient selection. "I don't think we fundamentally changed what we were doing, but we understand now exactly what the FDA wants to see when we do the submission."

The only downside Reynolds notes is that the process takes time. Ideally, once the protocol is submitted a 45-day review clock starts ticking, but if outstanding issues arise there may be another submission, and a new deadline for review. "It can go on for a long time," he says, perhaps months, but he sees the ultimate value as saving time in the final approval process.

Popular, But Not Perfect

Sara Radcliffe, Vice President for Science and Regulatory Affairs at the Biotechnology Industry Organization (BIO) offers a broader industry perspective on SPAs. "I would say our companies have found the process very helpful, but it isn't perfect. Part of the difficulty arises just from the uncertainty of drug development."

According to Radcliffe, an applicant may have done their very best to identify the requirements for demonstrating safety and efficacy for a drug, but the FDA always reserves

the right to change its views should new information come to light. “That can be very frustrating for companies, but we understand that it may be a legitimate reason.”

Other problems may arise involving the level of detail or granularity in the assigned protocol. “Some can be very general, and then as you go forward questions can arise with the research that simply weren’t addressed in the SPA,” says Radcliffe noting that the assigned protocol may not allow for prudent detours along the prescribed course.

Radcliffe, who is responsible for developing and implementing BIO’s responses to scientific and regulatory issues thinks that on the whole, the SPA program is working—consider as evidence that the number of SPAs are going up. Requests increased for the fifth straight year, although at a slower rate from Fiscal Year 2006 to Fiscal Year 2007 (Fig. 1).

| Requests for Special Protocol Assessments | | | | |
|---|-------|-------|-------|-------|
| FY 03 | FY 04 | FY 05 | FY 06 | FY 07 |
| 293 | 346 | 396 | 406 | 456 |

Figure 1. Source: <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm081888.htm>

“One assumes that if companies didn’t find SPAs useful they would not be doing them,” she says. Further, during the technical discussions that preceded PDUFA reauthorization both industry representatives and the FDA agreed that more resources should be devoted to SPAs.

Given such interest, one might ask if there is a risk in not doing an SPA. “It depends on the area you’re working in,” says Radcliffe. “It could be much more valuable where there are significant uncertainties, for example, a cutting-edge area of research where there hasn’t been a product like yours going through the process before.” A company needs to discern if the FDA sees a straightforward pathway, or if there is sufficient uncertainty in the research program that could be ameliorated by submitting to the SPA review. Uncertainty may also exist in the mind of company investors—further motivation in considering an SPA.

Radcliffe sees the benefits of using a consultant. “I think it’s valuable to benefit from the experience of someone who’s been through the SPA process before and has seen how a number of these things have worked—and not worked. In larger companies there may be any of those people in house, but for smaller companies...reaching out to a consultant could be extremely valuable.”

Show Me the Money

According to Mark Monane, MD, Vice President and senior analyst in biotechnology and biopharmaceuticals, Needham & Co, New York, “Having an SPA in place is especially important if it’s the company’s first drug in late-stage development.” Other situations where an SPA is a desirable possession are when the drug entity in question is first-in-class, or has (or could have) orphan status designation. This is particularly true in oncology where drug development frequently explores uncharted terrain. “The SPA is very helpful because it lays the groundwork. It gives you a trail to follow,” he said.

Not that you still can’t get lost, he commented, saying, “Yes, the agreed upon protocol exists as a sort of contract with its itemized expectations, and you have to live and breath by this thing. But, as the trial develops and you want to make changes, those are harder to make because of the SPA.” According to Monane, there are fewer degrees of freedom with SPAs than if a company had proceeded on its own.

To be clear, an analyst is not privy to the SPA’s provisions, but it creates a comfort zone. “It’s like a recipe for a cake. It takes time, attention, and love to get the cake right.” However, the recipe isn’t enough, there still needs to be an effective team in place to do the work. “I definitely use the SPA as one of my check boxes,” he says, “You still have to execute, but it’s a nice place to start.”

Be Careful What You Ask For

In some cases, an SPA needs to be amended. An amended SPA is one of the features of the much publicized and torturous approval pathway that Dendreon experienced with Provenge.

Dendreon’s Chief Medical Officer, Dr. Mark Frohlich, tells the story: “In late 2005, based on information gleaned from our previously completed Phase 3 trial, it became apparent that overall survival was a secure endpoint for measuring efficacy in a therapeutic product that has delayed onset of action.” There was a less obvious effect on the criteria of time to disease progression, prompting investigators to alter their trial, D9902B—originally designed with co-primary endpoints of disease progression and pain—to then have overall survival as its main emphasis. Powering the trial for [cont. on pg 14 >>](#)

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