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The Science & Business of Biopharmaceuticals

## Preparing for Your First IND Submission: The Devil is in the Details

When preparing an IND submission, an open mind and ability to interact effectively with the FDA is just as important as a sound product

In the process of developing breakthrough biopharmaceuticals with profound therapeutic promise, the many detailed requirements for a successful investigational new drug (IND) submission may seem petty, but they are not. With an IND, you are essentially moving from the cloistered world of the laboratory into a highly regulated industry where details not only matter, but are also greatly magnified by the overriding requirements of safety and efficacy. Treat those details with forethought and you will eventually succeed. Treat them as an afterthought and all of your pioneering science, state-of-the-art technology, and therapeutic ambition could come to nothing. At the very least, your progress to market could be delayed significantly. And if, like most young biopharmaceutical companies, you are on a short financial leash, such delays can be fatal for securing additional funding.

Based on our experience working with biotechs and the FDA, we have found that by adhering to the following principles you can greatly increase your chances of a timely and successful IND submission.



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**Begin at the Beginning:** Many first-time applicants greatly underestimate the time that it takes to prepare and submit a well-designed, well-executed IND. From the time you have a genuine clinical candidate, you can typically plan on at least a two-year time frame to gather sufficient information to file an IND and submit it to the FDA. Companies that devote methodical, systematic attention from day one move far more efficiently toward clinical trials than companies who delay. Ideally, even before the research phase, you should study the relevant FDA instructions and forms for an IND submission, which

can be found on the FDA's web site, and determine how your organization can best meet those requirements.

**Do the Science Right:** The science behind the drug should be rigorous and so should the records of it. It is not unusual for products originating in discovery environments to be missing a detailed, well-documented historical chain of events, and hazy origins will often raise serious issues and not satisfy FDA reviewers. You must design and document a comprehensive list of all toxicity and other preclinical studies that will answer most of the critical questions about your product's origin, characteristics, safety, and efficacy in laboratory tests and models. If you don't have a pharmacologist on staff, you should seek help to make sure that you can demonstrate the pharmacology.

The failure to design, execute, and document the right studies from the outset can come back to haunt you—and set you back by years. For example, one biopharmaceutical developer, working with a promising reengineered cell line that produced a particular protein, mapped the genes but failed to do sequencing analysis of the genes because the organization didn't believe it was necessary. However, one persistent scientist insisted that without sequencing analysis, it was impossible to know if any mutations might exist in the construct. When the line was sent out for a nucleotide map analysis, it came back with several mutations in the gene of interest. If the organization had not discovered the mutations and had gone to the FDA two years later with their IND, the agency would have asked for that analysis and the developer would have been back at square one. Instead, the developer was able to reengineer the line early on, lost very little time, and was able to supply the FDA with all of the required information about the cell line.

Unfortunately, when some companies find themselves before the FDA with inadequate data, they go

into survival mode and defend the product or technology, arguing that the agency should approve the IND anyway. Doing this runs the risk of losing credibility with the agency on all counts. If you do the science right in the first place, you can avoid putting yourself in that position.

**Document as You Go:** Some first-time applicants wait until very late in the process to begin creating the IND application. You should write up each of the milestones required on the application as you complete them, instead of being forced belatedly to put together what is usually a voluminous document. The documentation will be fresh and you will have time to make sure that it is scientifically sound, addresses a medical need, and has a safety profile appropriate for the clinical indication. If your organization does not have prior experience with writing INDs, hire a professional contractor who understands the types of issues that the FDA often raises. This will be money well spent, because your IND document will be professionally prepared according to FDA expectations.

**Timing Your Pre-IND Meeting:** The pre-IND meeting offers an invaluable opportunity to familiarize the FDA with your company, the investigational drug, the benefits and medical need for it, and your understanding of the agency's requirements. This meeting is usually scheduled three to nine months before the IND submission. The closer you schedule it to the actual submission, the more thoroughly you should understand the biological process and possess the data to support it. Conversely, if you think you could benefit from FDA feedback earlier in the process, you should schedule the meeting far in advance of

the submission. You could emerge from the meeting with valuable advice about patient populations, additional animal studies, and precisely what the reviewers will be looking for. The agency is accustomed to both kinds of meetings.

In either case, you should have in hand a protocol, a clear idea of the indication for the drug, and GLP animal studies to support the indication. You should also have manufactured the drug under GMP-like conditions for clinical studies, have qualified analytical testing in place, and allow for at least six months of stability studies after manufacture.

**Regard the FDA as A Partner:** Some companies unreasonably dread meeting with the FDA, seeing it as an obstacle whose knee-jerk reflex is to say no. Protecting the public is a top priority for them, but they do so as highly knowledgeable, experienced scientists who may have more knowledge than you about your process. For example, a biotech start-up had included a compound in the downstream purification process to maintain product integrity. During a very early pre-IND meeting, an FDA reviewer asked if such a class of compounds had been used. When the company said yes, the reviewer pointed out that this caused a serious problem. The company removed the compound from the process. Without the pre-meeting and the knowledgeable reviewer, the company would have continued down the wrong path and been stopped later in the process.

**Check Your Ego—and Business Case—at the Door:** The objective of the pre-IND meeting should be to share with the FDA exactly what you have: scientific results, supporting data, and understanding of the quality and regulatory requirements. In addition to supplying

the "hard" data, you should also be cognizant of the "soft" side—the quality of your interactions with the agency, especially in this crucial first meeting. Don't be arrogant about the science or argumentative about issues that the agency raises. Because the review panels are assembled on an ad hoc basis, the discussion can sometimes feel like a PhD oral exam, but the intention is to arrive at a clear understanding of the issues. Similarly, the state of your funding has no place in the pre-IND meeting. Stick to the scientific and regulatory issues.

**Remember the Goal:** Having pursued rigorous science from the beginning, created the IND documentation throughout your progress, and benefited from the pre-IND meeting feedback, you are ready to submit the final application with all of its attendant and detailed documentation. Within 30 days of receiving your submission, the agency will either accept your clinical protocol and let you begin trials or it will ask for additional information for review. Even if you have taken great care every step of the way, it is likely that at some point either following the pre-IND meeting or the submission you will have to do some further work—conduct more basic research experiments to better understand your product, develop additional analytical tests, conduct additional animal studies, or modify your clinical design. Such requests are opportunities to fine-tune your product and protocol on your way to an IND that will take you successfully through Phase 2. In fact, the best way to get the most out of the IND submission process is to see it as a way of helping you produce the best product you possibly can. ♦

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