PharmTech.com
ADVANCING DEVELOPMENT AND MANUFACTURING

Early Development Challenges in IND Applications

Meg Rivers

Collecting relevant data, planning ahead, and communicating with regulatory bodies in pre-IND meeting programs can help companies to avoid roadblocks in IND applications.

Prior to submitting an investigational new drug (IND) application to FDA, there is much for companies to plan and consider in advance. Collecting the appropriate data and determining just how much data are required to prove a drug product is reasonably safe for initial testing on humans are some of the challenges facing companies in the pre-clinical stage of development and planning for IND activities.

According to Mara Holinger, SVP, regulatory affairs, Veristat, the drug product, biologic, or other proposed assets should be tested in *in vitro* and *in vivo* to demonstrate that the product is efficacious in a therapeutic model.

"Next, or in parallel, a contract development and manufacturing organization (CDMO) needs to be selected," Holinger continues. "The drug product formulation needs to be carefully considered and then manufactured per good manufacturing practice (GMP) standards. The drug product will need to undergo toxicology studies, typically in two animal species, for both acute and repeat dose testing. These studies are generally required to be conducted per good laboratory practice (GLP) standards."

Additional testing that might be required, depending on the product type and indication, include the following:

- genotoxicity
- reproduction toxicity
- carcinogenicity.

It is also essential that all necessary information is collected for the drug substance, the drug product, and the non-clinical and clinical investigations, Paola Tocchetti, senior VP, head of global regulatory affairs, Evotec, explains. Some of the required information includes an investigator brochure, a clinical protocol, all IND sections in electronic common technical document (eCTD) format.

"It is our best practice to have all these documents included in an internal tracking system, an 'IND tracker' allowing us to follow the progress of the IND documents preparation according to the set timelines. The IND tracker also enables us to order priorities for any critical paths," says Tocchetti.

Planning for an IND

As might be expected, some believe the best time to plan for IND activities is as early as can be managed.

"The regulatory strategy should be in place as early as possible in the development process—ideally at the step when the candidate is nominated for development," says Tocchetti. "This is then followed by the IND edition, which requires the drug substance, drug product, and non-clinical reports. The health authorities' regulations are the driving factor for the drug development process; for example, compendial tests from [the United States] and *European Pharmacopoeia* and regulated toxicology programs to support the first-in-human study must be performed."

Meanwhile, Kevin Hennegan, senior regulatory strategist, Veristat, shares that there isn't a single answer for when to start planning for an IND application, explaining that most companies should think about a regulatory plan once there are data to support a possible clinical benefit for an investigational product.

"To set the IND up for success, I think the two most important things a company can do are to engage an experienced regulatory professional (either an employee or a consultant) who can help you navigate the process; and take advantage of the free advice offered by FDA through the pre-IND meeting program," Hennegan explains.

But the data are not the only important factor for INDs. A clear presentation of data is also critical. Hennegan

adds that the success of an IND submission depends largely on how clearly the data are presented—in addition to complying with regulatory guidance.

"For a regulatory reviewer, it is important that the document that he/she receives is coherently worded, linguistically correct, [and] consistent in terms of content and connection between the different sections. The goal is to provide a document that the reviewer 'enjoys' reading," says Tocchetti. "We also find that the timely and accurate input of all the R&D functions and the integrated management of their different contributions is crucial to ensure the success of an IND submission."

Pitfalls and misconceptions

From a manufacturing perspective, selecting a CDMO is a common pitfall. According to Hennegan, CDMOs can create significant delays in programs if they are low-performing.

"One other pitfall that is sometimes missed is not thinking product quality through all the way to delivery to the patient," says Hennegan. "If there is a dilution step or a novel (i.e., investigational) device required for delivery, you will need to provide data that those processes do not adversely affect the product."

Hennegan further breaks down potential pitfalls into non-clinical and clinical:

- **Non-clinical:** One pitfall is species selection. Costly additional studies can result from failing to perform toxicology studies in a relevant species. Meanwhile, costs can also be increased—without adding value—when selecting burdensome species. Selecting the best species to use should be discussed in a pre-IND meeting.
- **Clinical:** Measures must be put in place to mitigate risks to the study subjects—such as frequent vital sign assessments, safety labs, follow-up visits, and rules for stopping a study—which can be done through risk analyses of the first-in-human protocol.

Tocchetti adds the most common pitfalls they have come across:

- The reviewer can't determine if the administration of a drug product in the clinical study is safe due to a lack of information in the IND.
- The most recent FDA and European Medicines Agency guidelines aren't adhered to when designing the nonclinical development.
- GMP and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines aren't followed, and a reason why the rules were not followed isn't documented properly.
- The quality level of the drug substance and/or drug product quality level isn't sufficient to administer it to humans.
- The findings of toxicology don't support dosing in humans.

Moreover, one significant misconception for IND applications, according to Holinger, is the turnaround time.

"[I've] worked with several sponsors that believe the IND writing and submission process can be completed in a month or two. If a sponsor is starting from scratch (does not have a previous IND to reference), it typically takes four to six months to write an entire IND, pull together all of the documents, and publish/submit the IND," says Holinger. "Another misconception I've come across is the assumption that an IND is a single document. INDs need to comply with eCTD standards including administrative information (module 1), summaries (module 2), CMC/quality (module 3), non-clinical testing (module 4), and clinical (module 5)."

Pre-IND Meeting with FDA: What to Expect

Pharmaceutical Technology interviewed Paola Tocchetti, senior VP, head of global regulatory affairs, Evotec, and Kevin Hennegan, Senior Regulatory Strategist, Veristat, on investigational new drug (IND) applications, specifically preparing for a pre-IND meeting with FDA.

PharmTech: What does a pre-IND meeting with FDA look like? What needs to be prepared in advance and when would this meeting be advantageous?

Tocchetti (Evotec): It is always advisable to meet with the FDA before starting an IND submission, especially if specific concerns or issues arose during the drug development process. This is particularly applicable in cases where guidance cannot be fully applied (i.e., drug substance or drug product manufacturing and controls). During the pre-IND meeting, a company can also discuss with the agency the human trial study design, the rationale for the initial starting dose, and/or its dose escalation criteria. This allows for a more streamlined IND submission.

A pre-IND meeting is, in our experience, an integral part and needs to be well prepared. The procedure for the pre-IND meeting has specific timelines: a meeting request must be sent to FDA at least 60 days before the proposed meeting date. Then, 30 days before the meeting, the sponsor should send the briefing document. Between seven days and 24 hours before the meeting, FDA sends a written response to the sponsor. The sponsor may decide to cancel the meeting if the written responses are considered exhaustive or keep it and discuss any specific clarifications on the feedback. After 30 days, FDA will provide minutes of the meeting. It is important to allow sufficient time from the pre-IND meeting to the IND to incorporate FDA suggestions into the IND submission.

Hennegan (Veristat): The pre-IND meeting is an opportunity for sponsors to talk to FDA about how existing guidelines and regulations will apply to their unique program and to discuss any alternative approaches the sponsor is considering. You will need to prepare a short list of questions. (Some FDA divisions limit sponsors to no more than 10 questions. Other divisions are more flexible, but we recommend no more than 20.) The draft questions will be submitted with your meeting request. You will also need to provide a briefing package that summarizes the available data on your product and the development context. Briefing packages are usually submitted ~30 days after the meeting request, but in some cases (e.g., COVID-related products), the meeting request and briefing document are submitted concurrently.

The pre-IND meeting is advantageous for most novel products and new molecular entities. It is particularly useful for sponsors who are relatively new to product development.

– Meg Rivers

Excelling in the IND application process

"Companies who excel [in the IND application process] have an integrated and multidisciplinary approach to IND planning and execution," says Tocchetti. "Thus, a tightly integrated approach and expertly coordinated delivery strategy enable them to carefully perform risk-management and rapid decision-making. The increase in quality allows for timely delivery of a robust and comprehensive regulatory data package for IND submission without ever needing to compromise on quality because of lack of time."

In addition, the probability of a successful IND is increased by running a pre-IND meeting with the relevant regulatory agency, such as FDA, according to Tocchetti.

Proper planning and project management, according to Erin Flynn, regulatory strategist, Veristat, are also key to excelling in the IND application process.

"Proper planning and project management are critical aspects of IND preparation that are often underrated," says Flynn. "The IND is a granular collection of documents that can sometimes be composed of upwards of one hundred individual documents, with multiple authors, and often with overlapping review cycles. It is imperative that all authors are aligned on product-specific details in order to maintain consistency throughout the IND and present the best face forward to the FDA. Project management is also key. It can be easy to get off track or overwhelmed by the sheer number of documents to prepare; so, effective tracking and timeline management streamline the IND preparation process."

IND applications expected to decrease

When looking ahead for 2022 and beyond, both Holinger, Hennegan, and Flynn predict the number of IND applications for COVID-19 vaccines will decrease. In addition, they predict a potential increase in the number of INDs for the treatment of COVID-19. Furthermore, they anticipate that trends in existence prior to the pandemic will re-emerge, such as an increase in INDs for personalized therapies, along with a general increase in INDs for mRNA-based products.

Meanwhile, Ralf Geiben Lynn, PhD, MBA, senior business development director, Evotec, foresees regulatory changes for large molecules.

"As more and more innovative treatments arise, we expect that the FDA guidance documents in non-traditional non-small molecule fields like biologics or gene-therapy products [to] evolve and mature," says Lynn. "Thus, it is expected in the future, that the sponsors and specialized CROs will continue to keep up-to-date with these new treatments."

Where the future of IND applications is headed, only time will tell. But one trend is clear: planning ahead whenever possible has the potential to provide a positive impact on INDs and their success rate. **PT**