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Sterile formulation strategies to shorten timelines for first-in-human studies

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Abstract

In the long and costly path to market, early development decisions to prepare a molecule for its clinical journey are among the most critical. Creating a complex formulation from the start can potentially add challenges and bottlenecks that may slow your path to market in later phases. On the other hand, moving too quickly and not gathering sufficient data along the way can make expediting timelines a challenge. Additionally, sterile injectable drugs sometimes call for unique manufacturing and packaging requirements that must be taken into consideration during formulation development. That is why it is important to adopt strategies that create simple but stable formulations for your sterile injectable, thereby establishing a solid foundation for the entire life cycle of your product.

Align formulation development with clinical trial objectives

To achieve the right balance between product quality and speed, a formulation must be developed to align with the objectives of each clinical trial phase. This can be done only after you identify a target product profile as well as the must-have requirements for each phase of development. Because the primary objective of phase I clinical trials is to test safety and determine the most appropriate dose, a formulation should be prepared with the understanding that a range of doses will be administered. Preclinical trials must demonstrate sufficient data on the toxicity and pharmacokinetics (PK) of the active pharmaceutical ingredient (API) in at least two species to determine whether to proceed with a trial in humans. Safety and tolerability of the API in healthy volunteers or patients is measured in Phase I.

When moving into Phase II, the goal is to assess the API's effects against a validated clinical endpoint. While some sponsors may want a single, clinical trial material batch, another option is to make only smaller batches that are utilized as enrollment increases throughout the trial. The formulation requirements moving into Phase III change significantly due to the increase in clinical trial participants and validation requirements related to stage gates of entry into each clinical phase. The number of patients enrolled for each phase will vary depending on the indication.

Increase speed to market by mitigating risk

When developing a sterile injectable drug, all existing product development data from pre-formulation development screenings as well as other studies that have been completed should be collected and considered. Assessing the existing data can help shorten timelines and reduce cost by eliminating repetitive work conducted up to that point. There are several studies and aspects of development to work through on the road to first-in-human (FIH) studies that can be broken into two main categories: preclinical formulation work and process development. Preclinical work encompasses the proof-of-concept studies, including the bench work on both the formulation development and analytical sides. Process development begins once a stable formulation is identified.

The goal of process development is to confirm that the formulation is robust enough to be managed throughout compounding, filtration, and aseptic filling. The development work executed in the non-GMP setting will flow directly into the processes used to prepare FIH clinical material. As part of preparation for FIH trials, phase-appropriate analytical methods must be established. A plan for clinical labeling and distribution should also be considered. To reduce the overall timeline, many of the activities mentioned above should occur simultaneously. A good program manager is an asset when establishing timelines and organizing the required activities for a successful clinical product launch.

How does Thermo Fisher Scientific develop a formulation?

While many factors must be considered during formulation development, it is the existing data on the molecule that drives the decision-making process. Three simple approaches can also be applied when developing sterile formulations:

1. **Avoid reinventing the wheel.** Whenever possible, use approved excipients and standard processes and only move to a novel formulation approach if others fail.
2. **Start with the end in mind.** Consider how the product will be filled and administered. Ensure the concentration targets match the anticipated dose, and develop a process that is scalable and able to be validated.
3. **Do not overcomplicate the process.** Think about how likely it is for a lengthy, multi-step process to be approved by the FDA, and consider whether the engineering and operations teams will be able to manage a complex process and formulation.

Initial studies performed should include solubility and then move on to excipient and buffer screening. The goal for both is to identify whether a stable liquid formulation can be prepared and to understand which matrix of excipients and buffers create the most stable formulation. Typically, several prototype formulations should be created and evaluated for short-term accelerated stability. To limit the number of prototypes, a design of experiment (DOE) can be performed. A DOE can also be used in cases where API is limited.

After the prototypes are evaluated, the top one or two should be chosen for scale-up and more formal stability studies. The scaled-up batches are used to develop and optimize the clinical batch process as well as the formulation and process parameters. Oftentimes, biological products or large molecules are delivered to the drug product site as frozen solutions that are ready to fill. Typically, little formulation work is required for these products, although some may be diluted prior to filling to achieve the appropriate concentration for the dosing strategy. For these molecules, a stable formulation has often been developed upstream at the drug substance facility. However, there may be process studies required to evaluate any risk associated with production of the first clinical batch.

Practical considerations during formulation development

Once proof of concept is complete and a promising formulation identified, decisions about how to deliver the drug product to the clinic must be made. These include the concentration, the dose, the fill volume, and the batch size needed to begin the batch readiness process. Batch readiness includes preparing specifications for drug substance and drug product, any required in-process testing, methods for those tests, batch records, and other documentation required for GMP production. Data from the formulation development process will often drive many of the parameters for clinical manufacturing.

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For Phase I dose escalation studies, the range of dosing should be evaluated to determine the best combination of concentration and fill volume. The goal, if possible, is to limit waste in the clinic while also reducing the number of batches or various concentrations manufactured to support the range of doses. Oftentimes, customers think they need multiple concentrations or various fill volumes. It may be more efficient to prepare a single concentration and fill volume and then utilize partial vials for the low dose and multiple vials at the highest dose. After concentration and fill volume are determined, the number of vials needed for the FIH study needs to be calculated. When estimating the number of vials required, in-process and release testing must be accounted for. Additionally, material for line losses, microbiological testing, and stability studies should also be included in the estimate.

Considerations for sterile dosage forms

To reduce timelines and utilize the most economic option, glass vials are the preferred component for FIH studies of sterile injectable drugs. In general, glass vials are readily available and less expensive than syringes, cartridges, or other non-glass components. Vials and rubber stoppers are a common configuration that are typically already qualified, which can eliminate the need for capital expenditures, container closure testing, and other expensive and time-consuming activities. There may be some cases when it makes sense to use a non-glass vial for stability purposes or even a syringe if the timeline to commercial is fast tracked. In any case, the component selection should be driven by the timeline, route of administration, and the regulatory path to commercialization.

Another important consideration when attempting to reduce the timelines to FIH studies is recognizing that the product is not bound by the initial presentation and additional changes at Phase II or even Phase III can be made. In many cases, the fastest way to get to the clinic is to supply a frozen liquid vial. A frozen liquid presentation may be used when stability is unknown or when stability information is limited. As more stability data is available, it will determine whether to move to a liquid refrigerated vial or a lyophilized presentation.

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Studies to support changing the presentation may occur concurrently with Phase II so that, by Phase III, the path to a commercial product presentation is clear. The Phase III product should be identical or very close to the commercial presentation, especially when timelines are expedited. Format changes should be considered when the goal is to extend the product shelf life or ease the use of the product by the clinician or patient. When moving from a vial to a syringe or cartridge, additional stability studies are required to ensure the formulation is stable in the presence of new contact materials, such as silicon and tungsten.

As products move through clinical phases, additional process studies, such as filter validation, extractable and leachable studies, contact part compatibility, mixing studies, shear stress evaluation, and others may be required. A risk assessment should also be completed, to ensure that gaps in data are not apparent due to the expedited timelines.

Let the data be your guide

Using a risk-based approach during formulation development prevents critical errors that could delay commercialization of your product. Collecting valuable data along the way during clinical trials will help support the safety and stability of the drug product. When timelines are expedited or products fast-tracked, very few clinical batches are made.

In those cases, gathering robust data from the start is even more important when presenting an application for approval from regulatory agencies. Allowing the data to drive decisions along the development pathway is key to a successful clinical program and paves the way for commercial launch.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 55 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Christy Eatmon supports the Global Sales and Business Development teams in providing technical support, designing strategies and supporting new business opportunities for Thermo Fisher's sterile manufacturing business. Christy has more than 15 years of experience in the pharmaceutical industry with an emphasis on process engineering, product development, aseptic manufacturing and filling. She has working knowledge of all phases from drug discovery to sterile product commercial manufacturing with expertise in small and large molecule sterile formulation. Previously, Christy supported the Greenville, North Carolina, site as a Senior Principal Scientist in the Commercial Operations and Pharmaceutical Development Services areas.

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