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MAXIMIZING DRUG FORMULATION FOR FIRST-IN-HUMAN TRIALS

The Key Role of Formulation in Drug Development

The main objective of first-in-human trials (FIH) is to determine the starting dose of a new drug, one that is low enough to provide minimal to no safety and toxicity risks and allows the highest dosage/benefit for the intended trial. The manufacture of the drug product for clinical trials is of critical importance, as the formulation, manufacturing, and assessment of a drug candidate during FIH trials can be contributing factors in whether the drug safely provides the correct dosage and, ultimately, gains regulatory approval. Decisions made during early phase development, when the compound is being used in a clinical research setting, provide significant learnings for its progression through later phase research. Integration is key – ensuring that information gathered at the clinic is efficiently incorporated into the manufacturing process is a major contributor to the goal of achieving marketing approval.

An integrated approach, which combines formulation development, GMP manufacturing and release testing, and clinical testing functions/workflows has been proven to reduce timelines while improving decision making. Using such an approach, initial batches of drug product are manufactured, tested/released, shipped to the clinical facility and administered to subjects within a few days. This real-time, adaptive manufacturing strategy is applied to the whole early drug development cycle, so that live clinical data drives decision making.

Additionally, certain processes can run in parallel on the program's critical path. For example, clinical dosing can start with a shorter product shelf life and, as a result, reduce CMC data packages. ICH stability studies can run concurrently with dosing, not impacting the timelines. In addition, as drug products can be manufactured on a small scale, the development of pilot-scale manufacturing can be removed from the planning.

When processes such as these are in place, cycle times between production and dosing are reduced. A product can be rapidly made and tested, and interim pharmacokinetic (PK), safety or pharmacodynamic (PD) data reviewed and used to determine parameters for the next phase of clinical study. This means that the data on a drug product dose can influence the drug product composition selected and manufactured in any subsequent dosing period, on a seven-day to fourteen-day cycle.

Using human clinical data to drive and inform decision making can significantly improve the accuracy of formulation evaluation. Successful products from the development program are identified, and sent for regulatory approval based on batch analysis and short-term stability data for demonstration batches of candidate formulations. These candidate batches are prototypical of potential clinical formulations, providing proof to regulatory authorities of the feasibility of batch manufacture, specification achievement, and stable product availability, maintained until dosing is completed.

While the early clinical assessments are ongoing with the initial FIH drug product, concurrent evaluation of potential issues that may arise in later development should be undertaken. A two-pronged approach allows for speed at FIH without jeopardizing later phase requirements.

Formulation

The first step on the pathway to FIH clinical trials is formulation development. Generally, it is advisable to develop a dosage form that can be produced efficiently and cost effectively, to established quality specifications; simpler dosage forms like oral liquids, powders, tablets, or capsules are favored. Among the favored dosage forms, there are advantages and disadvantages to each. For example, tablets can have a longer shelf life and can accommodate a higher dose of active ingredient than capsules, while capsules are fast acting and can provide a higher drug absorption rate. Some advanced drug delivery systems, such as nanoparticles, require more complex formulations and manufacturing processes, and thus involve increased manufacturing costs, particularly in later development stages and commercialization.

Many of the drugs that enter development fail, even if they make it through FIH studies. Some of the high attrition rate can be attributed to the fact that key performance characteristics – such as solubility and bioavailability – are easily achieved in simple FIH formulations but challenging to replicate in more complex dosage forms for late-stage trials and commercial use. When creating a FIH formulation, it is important to keep in mind the rigors of later stage development and eventual market availability.

Bioavailability and stability are two key considerations for FIH drug product formulation. Adequate planning and cost/benefit analysis for different options are important, as they often present challenges for later stage development.

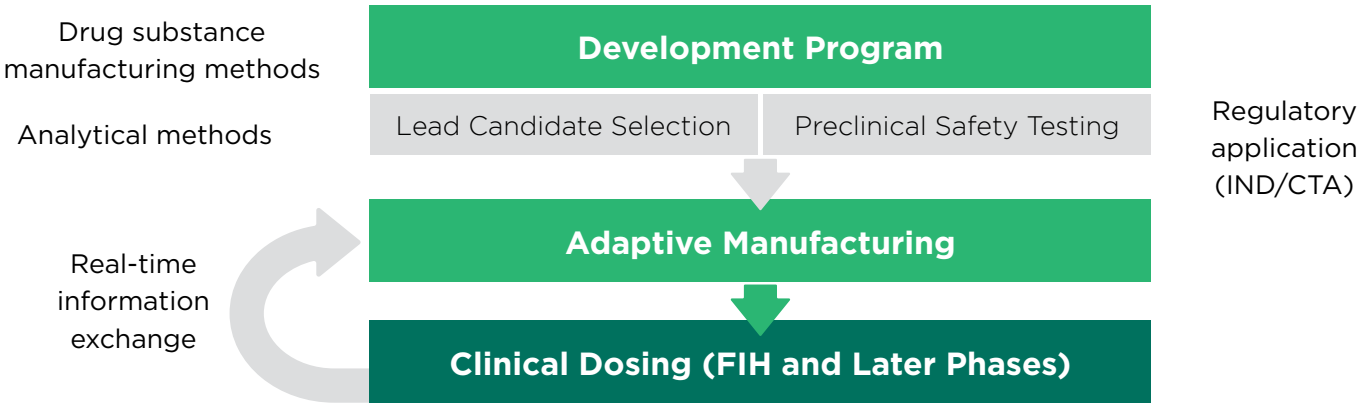
Bioavailability is critical to ensure adequate exposure to the drug; important throughout the phases of development. Weighing the advantages and disadvantages of different dosage forms early in the development process informs planning in later stages. If there is concern that a drug candidate may not demonstrate appropriate bioavailability, it can be a good investment to develop more than one dosage form, so that changes can be made without significantly impacting timelines.

Stability – FIH formulations only need to be stable for the duration of the study. Typically, regulatory submissions include data supporting seven days of stable shelf life. However, formulations used in late-stage trials need to demonstrate long-term stability, so it is best to consider this factor at the start.

In order to achieve satisfactory performance, the formulator may vary composition and processing:

Composition – Finding the best combination of active pharmaceutical ingredient (API) and excipient minimizes waste and dosage form size. The excipients selected for use in FIH formulations are typically chosen to minimize API degradation and ensure the appropriate release profile and stability characteristics. Excipients should be chosen based on the dosage form being used to help with characteristics like compatibility, hygroscopicity, flowability, and bulk density for the formulation.

Processing – FIH formulation efficiency requires a cost-effective, fast manufacturing process, which is flexible for scale-up in later phases and commercialization. When developing a process for a FIH formulation, it is important that the process can be performed in a robust fashion for small trial batches, and also can be scaled so that a similar process is implemented for large-scale manufacturing and commercialization.



The Impact of Formulation on Subject Safety

Subject safety is always a primary concern in planning clinical studies, and particularly with novel drug products entering FIH trials. The use of single ascending dose (SAD) and multiple ascending dose (MAD) cohorts, as well as the employment of adaptive protocols and sentinel dosing are part of the established safety protocols for Phase I studies.

If the candidate drug is considered high risk based on data from preclinical trials, it is preferable to formulate for intravenous administration. A slow intravenous infusion can easily be stopped if serious/severe adverse reactions occur. Likewise, dose escalation needs to be considered during manufacturing to fit the planned dose levels in the FIH study and the data gathered from sentinel dosing. If adjustments are needed based on data from the initial dose plan between cohorts, it is important to be prepared with a plan to titrate dosage, or reformulate the product to ensure maximum effectiveness with minimal safety concerns.

Meeting Regulatory Requirements

Regulatory requirements for novel pharmaceutical products are a major consideration in planning. Some of the critical elements include:

- FDA, EMA, MHRA, and Health Canada labelling requirements
- Import/export permits and licensing
  - Schedule I permits (if and as applicable)
- Special storage and handling requirements
- Lead time for drug shipments

Each development program will have its own unique set of parameters and logistical requirements. It is recommended to perform a thorough feasibility analysis during the "request for proposal" phase of the process, using the specifics of the program in question to establish the optimal processes and practices that meet all the regulatory requirements, and maximize opportunities for successful trial conduct.

Another step that can help address any potential regulatory concerns is a comprehensive scientific and medical protocol review, ensuring that all preclinical safety signals and other available data is fully addressed by the proposed FIH trial package.

Thorough pharmacy manual preparation is also a key component of a successful FIH strategy. Maintaining an accurate and thorough record of pharmacy compounding methods can be beneficial if changes to dosing and formulation are contemplated, or required.

The importance of ensuring that your CRO/CDMO partner works from harmonized SOPs based on GMP principles also should not be overlooked. When GMP principles are the basis of clinical pharmacy processes, the majority of study-related changes to compounding, such as preparation, blinding, and dose changes, can be handled at the clinic pharmacy. When a modification is out of scope for the pharmacy, a GMP-certified CDMO site should be ready to perform any necessary full-GMP changes, and rapidly deliver the drug product to the clinic. When methods and customizations from each stage are guided by GMP principles, and shared between the key internal stakeholders. It enables complete knowledge transfer and resource efficiencies.

Throughout early phase human drug development, the integration of GMP-based, GCP pharmacy on-demand with accredited GMP CDMO capabilities maximizes a timely program completion. With appropriate foresight and planning, simple or complex formulation and dosing changes, before or during study conduct, can be seamlessly managed and synchronized within your original timeframe.

CASE STUDIES

Pharmacy Case Study – Supporting Regulatory Approval

- Novel API in powder form with no oral formulation.
- Phase I, FIH, double-blind, placebo-controlled adaptive SAD/MAD, with sentinel dosing

An oral suspension formulation of the investigational product (IP) had to be developed for dosing. Multiple mock preparations, at different dose levels, were prepared to measure concentration, microbiological activity, IP stability, etc.

A placebo also needed to be developed, as there was no commercially available preparation that had similar visual, taste, texture, and precipitation properties as the novel IP. Altasciences' pharmacy team was able to develop a placebo that met all the criteria, including masking the taste of the IP with a flavoring.

Details of the development were captured in a comprehensive pharmacy manual, which played a role in the study approval. Typically, regulatory authorities do not request pharmacy manuals; however, because the nature of the IP, they did in this case. Following their review, the proposed dosing levels were changed, and due to the flexibility and adaptable nature of the compounding procedure, the requested changes were implemented without affecting critical timelines.

Manufacturing Case Study – Mission Impossible to Possible

- Formulation and manufacturing for a small molecule API.

The initial project parameters were to develop the product for a FIH study, with proof of concept in mind. No previous formulation work had been conducted; the drug product needed to be nano-sized for optimum bioavailability.

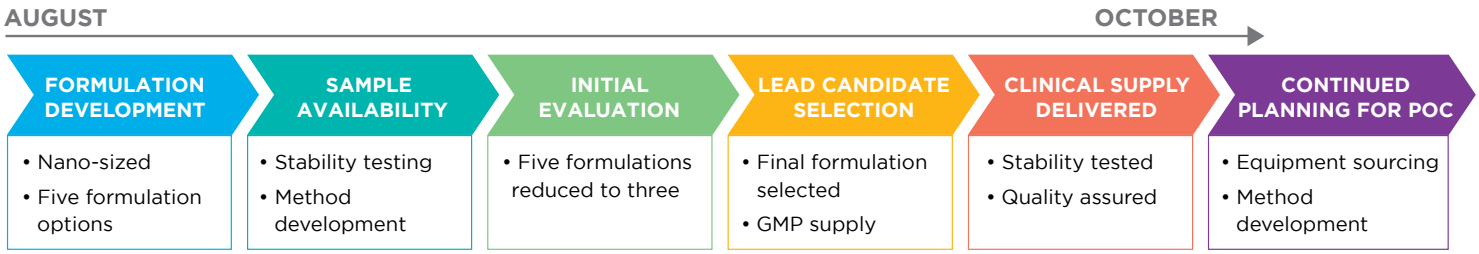
The project had a two-month timeline:

- Launched first week of August
- Clinical delivery required first week of October

Five formulations were developed in the lab. The samples were tested in concurrent processes:

- Accelerated stability testing for lead candidate selection
- Method development, impurity testing, assays, etc.

After two weeks, all five formulations were evaluated. Three were selected to continue the process, scheduled for an additional two weeks. At the end of the four weeks, a final formulation was selected for the FIH study. The previously developed methods were utilized for GMP supply, and production started the second week of September. Lab- and QA-ready, the final product was delivered for dosing at the clinical pharmacology site, on time.



Continued efforts for later phases (six months) to proof of concept:

- Analytical lab continued developing methods.
- Manufacturing sourced equipment and added capabilities.

Integrating to Maximize Chances for Success

Significant benefits can be realized with Altasciences' Proactive Drug Development approach of integrating GMP manufacturing and clinical testing. Shorter timelines, reduced costs, and improved flexibility are achieved with real-time drug product manufacture, as the development team can evaluate and optimize new formulations in the clinic, based on human data. When clinical trial teams work closely with those involved in formulation and manufacturing process development, collaboration and data sharing minimize risk and help reduce delays. Product development can be started when a quality API is ready, the clinical study can start as soon as regulatory approvals are received, and the product is released.

If you are interested in maximizing efficiency and optimizing processes for your early phase drug development, contact us today. With Altasciences, you will work with an integrated CRO/CDMO that can deliver on opportunities, minimize handoffs, maximize information sharing, and drive your projects forward in the most seamless, efficient manner.

ALTASCIENCES' RESOURCES

Webinar

Overcoming the Challenges of Manufacturing and Clinical Trials

White Paper

Utilizing Nano Particulate Formulation in the Delivery of Poorly Soluble Drugs

Brochures

Manufacturing and Analytical CDMO Services Overview

Pharmaceutical Manufacturing Services

Pharmaceutical Analytical Services

Video

Our Comprehensive Manufacturing and Analytical Solutions

Quick Chat with Ben Reed, Executive VP, Operations

Blog

Improving Solubility of Molecules via Nanomilling

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ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.