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CONSIDERATIONS TO ACHIEVE OPTIMAL PRECLINICAL FORMULATION AND DRUG PRODUCT MANUFACTURE

Formulating and manufacturing drugs for preclinical testing is an early, crucial step toward human trials. At the preclinical stage, the goal is to maximize exposure for safety testing, formulating to the limits of solubility and maximum volumes. To optimize the formulation for preclinical testing, one must consider the route of administration, selection of excipients, stability testing, plans and options for scale-up, and contingency plans.

IN THIS ISSUE

We explore key considerations for successful formulation development and manufacture for safety assessment, alongside examining the strategies Altasciences employs to support sponsors.

See the case study on page 8 for details on how we produced a stable nanosuspension for preclinical studies.



INTRODUCTION

Preclinical manufacturing involves various sub-processes, all of which are critical in overall drug development.

- **Formulation Development:** the drug's delivery system is designed, such as a liquid, tablet, capsule, or injectable dosage form.
- **Manufacturing Process Development:** the process for producing the drug at scale is established.
- **Scale-Up:** increasing manufacturing process to produce larger quantities of the drug.
- **Process Validation:** the manufacturing process to ensure it consistently produces the desired product is validated.
- **Analytical Method Development and Validation:** methods for assessing the drug's quality and purity are determined and validated.
- **Stability Studies:** the length of time that a product will remain stable is determined, i.e., maintain the properties and characteristics it possessed at time of manufacture.

Thorough early analysis of the characteristics of the test article (TA) facilitates the transition from laboratory tests to GMP manufacturing, saving time and money, and avoiding the unnecessary use of animals.

Some of the key considerations are:

- stability of the TA in the proposed formulation matrix;
- chosen excipients and their underlying toxicity profile for the relevant preclinical species; and
- selection of the most appropriate vehicle for preclinical test models.

The common route of administration for preclinical testing is oral, due to its translatability to patients, typically liquid formulations that can be adjusted easily based on the weight of the selected test systems. If suitable exposure is not possible via the gastrointestinal tract, then intravenous or subcutaneous administration may be possible using solutions. For dermal studies, creams or gels are ideal since they remain at the site of administration for the intended duration, to generate adequate exposure to the formulation.

Many other dosage forms are possible throughout the development process, including nanomilled suspensions, solutions, creams, gels, powders, tablets, liquid- and powder-filled capsules, over-encapsulated capsules, and injectables. For more information on formulation considerations for first-in-human studies, consult [this issue of *The Altascientist*](#).

Whatever the route of administration, determining the maximum concentrations and the maximum volumes that can be dosed in the test species provides early data regarding the feasibility of achieving appropriate doses for clinical trials. Ensuring that the selected formulation can be scaled up throughout development is a key component of formulation planning.

CONSIDERATIONS FOR PRECLINICAL DRUG FORMULATION

Pre-formulation

Pre-formulation studies are mainly used to predict drug performance *in vitro* and *in vivo* via characterization of the physicochemical and mechanical characteristics of a drug candidate. Pre-formulation studies usually provide the following data:

- acid dissociation constant of a solution (pKa)
- logarithm of the partition coefficient (LogP) and distribution coefficient (LogD)
- pH solubility and stability curves
- solvent solubility
- particle size distribution
- hygroscopicity
- active pharmaceutical ingredient (API) solid-state stability under stressed temperature/humidity conditions
- melting point
- salts form evaluation
- polymorph and crystallinity
- forced degradation under different stressed conditions (light, heat, oxygen, pH, etc.)
- stability-indicating analytical methods for characterization of API
- impurities

This information helps determine the best approach for development strategies by allowing for some degree of prediction of the stability of a potential formulation throughout the development process.

Biopharmaceutical Assessment

The biological attributes of each drug candidate selected for further study are necessary for formulation development and appropriate dosage form selection. Attributes consist of, but are not limited to:

- compound dissolution, solubility, and stability in simulated gastric and intestine fluids
- enzymatic stability
- intestine membrane permeability
- modeling and simulation of animal and human PK and bioavailability

For oral compounds, a key feature of the formulation, once delivered to the gastrointestinal lumen, is the ability of the API to dissolve or disintegrate in order to be absorbed via the gastrointestinal membrane. Absorption is the first step to identify any potential limitations of a compound and provide early recognition of poorly performing formulations to be screened out.



Researchers in discovery organizations typically select drug candidates based on biological properties, such as binding affinity, potency, efficacy, cross-reactivity with target species for toxicological studies, and epitope recognition. However, to successfully transform a candidate into a drug, additional properties must be evaluated. These include:

- 1. Manufacturing Feasibility:** expression and purification yields, aggregation propensity, stability, and compatibility with *in vivo* conditions are assessed.
- 2. Formulation Ease:** ease of formulation for a specific route of administration are considered.
- 3. Safety Characteristics:** compatibility with *in vivo* environment, cross-reactivity, half-life, and immunogenicity are evaluated.

Developability assessment ensures that selected biologic drug candidates can be manufactured with a platform process, minimizing costly adaptations later in development. By addressing risk and optimizing safety and manufacturing properties, this process contributes to successful drug development.

PRECLINICAL DRUG PRODUCT MANUFACTURING

Several factors must be considered during preclinical drug product manufacturing. These include ensuring the drug's stability, bioavailability, manufacturability, and compliance with regulatory requirements. Each of these factors presents its own set of challenges. In fact, according to the U.S. Food and Drug Administration (FDA), about 50% of drugs fail during the preclinical stage due to stability issues.

Preclinical drug manufacturing, including materials and excipients sourced externally, must comply with Good Manufacturing Practice (GMP) guidelines, and meet stringent quality control standards and documentation requirements.

Materials used in GMP manufacture must be produced in controlled environments and will need to be available in sufficient quantity to support the planned studies. Excipients need to be screened to identify potential incompatibilities that affect the physical, chemical, microbiological, or therapeutic properties of the TA in dosage form. Whenever possible, it is recommended to choose common excipients, as their attributes are well known, and they are likely to be available from multiple sources.

Table 1. Commonly Used Excipients in Pharmaceutical Formulation

Class	Function	Examples
Buffers	Change ionic environment.	Acetate, citrate, bicarbonate, phosphate, acetic, hydrochloric, tartaric, or citric acid
Cosolvents	Solubilize by dissolving.	Ethanol, propylene glycol, glycerin, dimethyl sulfoxide and polyethylene glycol
Complexing agents	Increase water solubility of lipophilic compounds.	Cyclodextrins, hydroxypropyl- β -cyclodextrin) and sulfobutyl ester
Surfactants and micelles	Decrease precipitation, increase chemical stability, formation of micelles.	Cremonophor RH60, polysorbate, lecithins, and poloxamers
Emulsion systems	Used for poorly water-soluble lipophilic compounds.	Vegetable, soybean, corn, sesame, or olive oil
Nanosuspensions	Milling test item to a diameter less than 1 μm to improve solubility.	Not applicable

Drug formulation involves converting a TA into a pharmaceutical product with a formulation that can enhance a drug's stability and efficacy. The NCBI reports that up to 90% of new drug candidates in the discovery pipeline have poor water solubility, which can be addressed during drug formulation, to improve their effectiveness.

The formulation development process generally involves pre-formulation studies (studying the physical and chemical properties of the drug molecule), excipient compatibility studies, prototype formulation development (formulations are developed on a small scale and tested for stability and performance), scale-up, and stability testing.

STEPS IN PRECLINICAL DRUG PRODUCT MANUFACTURING



Scale-Up

According to a Journal of Pharmaceutical Innovation study, nearly 70% of scale-up processes encounter challenges that could potentially affect the drug's quality attributes, thus engaging with an experienced drug development partner that can navigate these challenges is essential.

Scale-up in preclinical manufacturing is a critical phase in the drug development process where the production of a pharmaceutical compound transitions from small-scale laboratory settings to larger, more industrially relevant quantities. This stage is pivotal for bridging the gap between the discovery of a promising compound and its evaluation in preclinical studies, which assess the drug's safety and efficacy in animal models before proceeding to human trials.

Strategies for successful scale-up include:

- Pilot studies: Pilot studies to test the scaled-up process under conditions that mimic commercial production can help identify potential issues before full-scale manufacturing begins.
- Process Analytical Technology (PAT): PAT tools for real-time monitoring and control of the manufacturing process can ensure quality and efficiency.
- Collaboration with regulatory authorities: Early and ongoing engagement with regulatory bodies can facilitate a smoother scale-up process by ensuring that all regulatory requirements are met from the outset.
- Flexibility in design: Manufacturing processes with scalability in mind allow for easier adjustments and optimizations as production volumes grow.

Typically, after R&D, a scale-up engineering batch is produced in the GMP manufacturing suites, which involves new equipment and a larger batch size. The engineering batch is there to help identify any scaling-up issues while providing enough material for process validation and stability studies, which are necessary to provide a baseline for data for clinical studies. If the engineering batch and stability data meet acceptability criteria, the engineering batch can be used in clinical trials if such usage was part of the initial drug development plan.

Manufacturing Process Development

Developing a manufacturing process for a drug involves determining the best method to produce the API and the drug product at scale. This process generally includes the following steps:

- selection of raw materials;
- determination of manufacturing conditions;
- development of a procedure for combining the raw materials; and
- establishing controls to ensure the quality of the final product.

One of the challenges during this stage is ensuring that the drug's quality attributes remain consistent throughout the scale-up process.

Process Validation

During validation, the manufacturing process is verified to ensure it can consistently and reliably produce the required drug product. This step is crucial in ensuring the drug's safety and efficacy; it is also a regulatory requirement. The FDA's guidelines on process validation outline a lifecycle approach which includes process design, process qualification, and continued process verification.

Analytical Method Development and Validation

In this step, methods for testing the drug's quality, purity, potency, and stability are developed and validated. These methods ensure that the drug product meets the necessary quality standards. Some of the methods developed in this step can form the basis of the bioanalytical assays used during clinical trials; keeping this in mind during analytical method development may help save costs and time.

QUALITY ASSURANCE AND CONTROL

Quality control in pharmaceutical manufacturing includes several tests and procedures.

- **Identity tests:** To confirm that the correct drug is being used.
- **Purity tests:** To ensure there are no contaminants in the drug.
- **Potency tests:** To verify the drug's strength and efficacy.
- **Stability tests:** To ensure the drug remains effective over time.

These tests are performed at various stages during the manufacturing process and on the final product, ensuring that every batch of the drug product meets the defined quality standards.



REGULATORY ASPECTS

The FDA has established [regulations and guidelines](#) that govern the drug development process; several of which have been mentioned above.

- The Investigational New Drug (IND) application contains data from preclinical testing and is necessary to advance drugs to human testing.
- GMP regulations ensure the quality of drug products.
- Validation that the manufacturing process can consistently produce the desired product.

Other countries have their own regulatory bodies and regulations and standards for preclinical manufacturing, such as those for the [European Medicines Agency](#) (EMA) in the European Union, the [Medicines and Healthcare Regulatory Authority](#) (MHRA) in the UK, and [Health Canada](#) in Canada.

The [International Council for Harmonisation](#) of Technical Requirements for Pharmaceuticals for Human Use (ICH) provides global drug development and registration standards, on which many countries have based their guidelines.

RISK MANAGEMENT

Risk management is a critical element in preclinical drug product manufacturing. It involves identifying, evaluating, and mitigating potential risks that can affect a drug products' safety, quality, and efficacy, and the safety and security of drug manufacturing operators and technicians.

Identifying and evaluating risks involves several steps:

- **Hazard Identification:** identifying potential sources of harm.
- **Risk Analysis:** estimating the likelihood and severity of each risk.
- **Risk Evaluation:** comparing the estimated risks against predefined risk criteria to determine their significance.

Some of the standard models used in the risk management process include Failure Mode and Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP), and risk matrices.

Risk management strategies in preclinical drug product manufacturing may include:

- **Risk Avoidance:** altering plans to minimize or eliminate risk.
- **Risk Mitigation:** reducing the impact or likelihood of a risk.
- **Risk Transfer:** shifting the risk to another party, often through insurance.
- **Risk Acceptance:** accepting a low impact or low likelihood risk, if the cost of mitigating it outweighs the potential impact.

ALTASCIENCES' CASE STUDY

Overview

A client contracted Altasciences for our Proactive Drug Development approach to rapidly get their new API through the preclinical development phase. Their goal was to develop a robust formulation at the maximum potency. At this point, a formulation needed to be developed from the ground up. This study was proposed to conceptualize and develop a stable drug prototype to be used in clinical trials.

Purpose

- Drug Development Phase: preclinical
- Class of Drug: small molecule, BSC Class II/IV
- Dosage form: nanosuspension
- Route of Administration: subcutaneous and intramuscular

Methods and Results

Our client presented us with an **API BSC Class II compound**, intended for extended release, with specifications about their requirements for a drug product.

A target product profile was quickly designed, with a clearly defined list of critical characteristics that reflected their specifications. Their goal was to develop a formulation prototype for preclinical work, including efficacy, pharmacokinetics, and toxicology studies.

Various dosage forms were summarized and proposed based on our formulation, manufacturing, and analytical capabilities. The client ultimately settled on a nanosuspension dosage for subcutaneous and intramuscular delivery.

Once critical parameters were identified, a list of potential excipients was provided to the client for experimentation. The excipients provided were expertly selected to provide the best-estimated results based on the appropriate drug delivery systems and manufacturing methods. All excipients provided had well-defined safety profiles and were recognized as safe by the FDA. Once approved, an excipient compatibility study was performed to determine if the API was stable in the presence of each excipient.

We determined feasibility around two critical factors: **particle size distribution** and **concentration**.

The initial experiment screened the approved surfactant excipients to best achieve the target particle size distribution. Our target was a D50<200nm and D90<1µm measure via laser diffraction. Solid API was suspended in an aqueous vehicle at a concentration of 20% w/w containing the different surfactants and 0.4mm YTZ grinding media. These formulations were subsequently milled for up to 48 hours and sampled at various timepoints.

Promising formulations were further investigated by repeating the milling at incrementally higher API concentrations up to 40% w/w. Analytical methods were developed in parallel with the feasibility experiments for particle size, zeta potential, and assay, in compliance with regulatory requirements. Successful formulations were then placed on short-term stability.

Prototype formulations were selected for scale-up and further optimized to meet all remaining parameters. Lead prototype formulations were then tested for appearance, particle size, assay, pH, viscosity, and re-suspendability.

With the data generated by the lead prototype formulations, we moved on to developing a robust and reproducible process necessary for large-scale manufacturing. The manufacturing process was scaled up and moved to our DeltaVita® milling equipment, and the process parameters (pressure, temperature, homogenization cycle, etc.) were optimized to reliably manufacture the nanosuspension. The pilot batch was used to support accelerated and real-time stability studies to assess the long-term stability of the nanosuspension, by evaluating the impact of various storage conditions on particle size and API stability.

How Altasciences Provided Value

The above-described approach to preclinical formulation development allowed us to rapidly optimize and produce a stable nanosuspension for preclinical studies.

ALTASCIENCES CAN HELP

Using advanced processes, we have formulated, tested, and/or manufactured nearly every pharmaceutical dosage form currently available on the market, including tablets, liquid- and powder-filled capsules, over-encapsulated capsules, nanomilled suspensions, creams, gels, powders, and terminally sterilized injectables.

Our team offers decades of expertise in drug development, manufacturing, and analytical services, including formulation development, Phase I through large-scale commercial manufacturing, and ICH stability storage and testing, to pharmaceutical and biotech companies worldwide.

We also provide analytical method development, qualification, and validation, and finished product and release testing.

We have a 99% on-time delivery record, and DEA licenses for drug Schedules I to V.

In addition to our CDMO services, our suite of solutions includes preclinical and clinical studies, as well as bioanalytical expertise. With our [Proactive Drug Development](#) approach, real-time communication and seamless collaboration provide optimal efficiencies for our clients.



ALTASCIENCES' RESOURCES

Webinar

[The Development of Nanosuspensions for Poorly Soluble Drugs](#)

Scientific Journal

[Nanomilling for Better Solubility and Improved Bioavailability](#)

Podcasts

[Key Considerations as You Move From Discovery to Preclinical to Clinical](#)

[Tips to Ensure Successful Formulation for Nonclinical Testing](#)

[Successful Manufacturing of Clinical Trial Supply](#)

Videos

[Step Inside Altasciences' Manufacturing Facility](#)

[The Art of Pharmaceutical Formulation](#)

Webpage

[In-depth information on our CDMO solutions](#)

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.

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