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Drug Formulation Development Process: Notes from a CDMO

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Introduction:

Drug Formulation Development Process: Notes from a CDMO

Identifying compounds and conducting formulation research in early-stage drug development is the beginning of the new drug development process. It's a step that can either propel you into a much smoother journey, or one that can end up derailing your trip to market and costing you millions in lost time and expensive re-work to find the right molecules.

That's where in vivo studies come in and the question arises: should our drug formulation process reside with an in-house team, or should we call an expert—an experienced contract development and manufacturing organization (CDMO)—to serve as our guide as we blaze a new trail in drug development?

In-house or at a CDMO, scientists have a big mountain to cross in the discovery formulation—they must identify a universal formulation for structurally similar lead series. This simplifies and limits the differentiating in vivo behavior. Researchers must understand and be able to solve challenges involved with discovery-stage formulations, such as limited quantities of potential drug molecules.

Other Risks Include:

- Drug substance purity and optimizing the therapeutic effect inside the body
- Physiochemical and structural properties of compounds and their interaction in the intended environment within the human body
- Determining the best solid-state form
- Limited accessibility to drug substances during early-stage development for solubility and stability testing
- Potential inaccuracy of solubility measurements through high-performance liquid chromatography (HPLC) assays



Chapter I:

Drug Discovery & Development Process Overview

From the beginning of the drug discovery journey to making it to its destination in the marketplace, **launching a new drug can take upward of 12 years and cost nearly \$1 billion.** In fact, for every 5,000-10,000 compounds that enter the development pipeline, only one crosses the finish line and gets approval.

A Guide to the Drug Discovery Process

What is Drug Discovery?

The goal of drug discovery is to identify a compound to cure or treat a disease. The process includes identifying therapeutic compound candidates, synthesis, characterization, validation, optimization, screening, and assays for therapeutic efficacy.

Stages of Drug Discovery Include:

✓ Target Identification

Before drug development can begin, the target therapeutic must be thoroughly researched, including the biological origin of a disease (gene/nucleic acid/protein) and the potential intervention or treatment. The ideal treatment should meet clinical and commercial requirements, as well as be safe and effective. Identifying the target compound often includes principles of molecular biology, biochemistry, genetics, biophysics, among others.

✓ Target Validation

Target validation involves verifying the structure activity relationship (SAR) or analogs of the small molecule, as well as developing a drug-resistant mutant of the target drug compound. Validation also includes analyzing the effects of overexpression of the target and monitoring its downstream effects.

Stages of Drug Discovery Include:

✓ Lead Identification

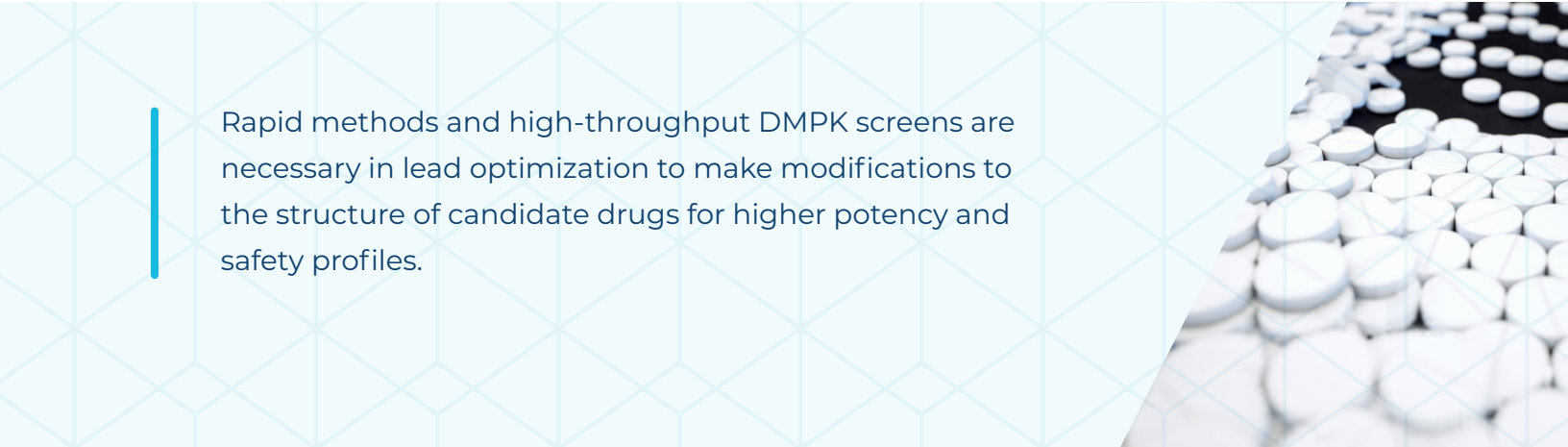
Identifying a chemical lead requires determining SAR, as well as evidence of in vivo effectiveness and engagement with the target. It must have appropriate selectivity, specificity and affinity for the target receptor, as well as the potential to bind to a specific target. The identified lead's absorption, distribution, metabolism and excretion should also be documented.

✓ Lead Optimization

An iterative series of synthesis and characterization of the potential drug is known as lead optimization. This helps researchers understand and identify the ways chemical structure and activity are related. Rapid methods and high-throughput DMPK (drug metabolism and pharmacokinetics) screens are necessary in lead optimization to make modifications to the structure of candidate drugs for higher potency and safety profiles.

✓ Product Characterization

Size, strength, weakness, shape, intended use, biological activity and toxicity are all evaluated and documented for product characterization.



Rapid methods and high-throughput DMPK screens are necessary in lead optimization to make modifications to the structure of candidate drugs for higher potency and safety profiles.

Drug Discovery & Development Process Overview

What Does Drug Development Entail?

After a compound has passed the investigative toll booths, it enters the process of drug development (which precedes clinical trials). The new drug development process involves several stages to make sure the medicine is safe, effective and has met all regulatory requirements.

✓ **Formulation and Development**

The formulation and development stage of drug development is where active pharmaceutical ingredients (APIs) are characterized to develop a stable, bioavailable and optimal dosage form for the intended administration type.

Considerations Include:

- Solubility
- Dissolution
- Stability
- Solid state properties
- Formulation services and capabilities
- Formulation development of new chemical entities (NCE)
- Optimization
- Process Development
- Novel formulations to improve delivery
- Controlled- and sustained-release formulations
- Self-emulsifying and colloidal drug delivery systems
- Sub-micron and nano-emulsions

✓ **Pre-Clinical Research**

Before a new drug compound enters clinical trials, pre-clinical research conducted with animals helps evaluate a drug's safety and potential efficacy in humans.

Pharmacology studies, which include the drug's pharmacokinetic and pharmacodynamic parameters, are crucial to determine the safety and efficacy parameters as they relate to absorption, distribution, metabolism and excretion.

Toxicological studies of the drug, which can be done by in vitro and in vivo testing, evaluate effects on cell proliferation and phenotype. Careful review of and selection of an animal species is important to accurately conduct a toxicity study.

✓ **Investigational New Drug**

Before clinical trials begin, drug developers need to file an Investigational New Drug Application with the FDA which includes pre-clinical and toxicity study data, drug manufacturing details, clinical research protocols, previous clinical research data (if applicable) and information about the developer.

Drug Discovery & Development Process Overview

✓ Clinical Trials

Clinical trials are conducted with people, and trial protocols and parameters are developed to answer questions about safety and effectiveness of the drug. Before a clinical trial begins, researchers outline participant selection criteria, length of study, number of participants, dosage, assessment parameters and how data will be collected and analyzed.



Phase 0

This clinical trial with 10 to 15 participants is the first-in-human testing done to determine dosage and how the body processes the drug (pharmacokinetic parameters).



Phase I

In this phase, the safety and dosage are evaluated using a small set of participants, usually ranging from 20 to 80 individuals with the targeted disease or condition. Dosage is adjusted to determine how much of the drug the body can tolerate, what is needed to address the disease/condition, as well as at what dosage side effects occur or increase.



Phase II

With a larger group of participants, usually a couple hundred, Phase 2 trials evaluate efficacy and side effects. Researchers use data from Phase 2 to adjust research questions, methods and design.



Phase III

With up to 3,000 participants, Phase 3 trials help identify less common side effects and potential long-term impacts of the drug. In addition to more in-depth drug safety information, further evaluation of drug efficacy is completed.

✓ New Drug Application

The New Drug Application (NDA) verifies that a drug is a safe and effective way to treat a certain disease or condition. Information in the NDA includes labeling plans, safety updates, drug abuse information, patient information, clinical trial results, institutional review board compliance information and directions for use.

✓ Approval

Once the FDA obtains a complete NDA, it thoroughly reviews all drug data and determines whether or not they will approve the drug. The review may take six to 10 months, and incomplete NDAs may be rejected.



Chapter II:


Why Drug Substance Characteristics Are Important

Physical and chemical properties of a drug substance, such as size, lipophilicity, ionization, hydrogen bonding, polarity, aromaticity and shape, have a direct impact on the drug product and formulation.

Getting the formulation (and all excipients used) correct makes sure the active ingredient is released as intended to provide the most effective drug substance. Negative interactions with any excipients can have adverse effects on shelf life and performance, which could potentially harm the patient.

Characterizing drug substance properties early is a critical step that helps avoid wasted time and money on formulation re-work, as potential issues can be addressed early in the formulation development process. Getting the right drug substance characteristics nailed down early on reduces development timelines, speeds up a drug sponsor's ROI and ultimately gets the medicine to those who need it more quickly.

Chemical properties can result in unintended reactions with other components in the drug product, which can cause harmful side effects, drug impurities and loss of efficacy.



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Why Drug Substance Characteristics Are Important

Issues in a Drug Substance's Physical and Chemical Characteristics Impact:



Solubility

The solubility of a drug substance in gastric juice or intestinal fluids shows the concentration limit for the drug within the GIT.



Dissolution Rate

Without the proper dissolution rate, the drug may pass through the body before it can have any type of therapeutic impact on the patient, or it may dissolve too quickly and become toxic. This makes the drug dissolution rate even more important to get the optimal absorption.



Powder Properties

With a direct impact on the dissolution rate, particle size and distribution (in addition to other powder properties and solubility), impact bioavailability.



Flow Properties

A drug substance's flow properties impact uniformity, segregation of components and potential product losses in processing equipment.

While drug substance characterization's impact on formulation is extensive, the emphasis and integration of characterization is not often incorporated into drug development at many CDMOs.

The purpose of exploring and documenting a drug substance's characteristics is to help researchers develop a strategy to address any weaknesses during the formulation stage. For example, a degradation study shows scientists a drug substance's stability under acidic or alkaline pH buffers, as well as the impacts of light, heat, humidity and oxygen, allowing them to protect the molecule through its formulation.

A drug product's physical properties, such as melting temperature, crystal structure, equilibrium solubility and mechanical properties lead to changes in formulation design, as well as dosage form selection.

Why Drug Substance Characteristics Are Important

The Challenges of Complex Molecules

Today's API molecules are increasingly complex, which is leading to more and more formulation problems that delay development and add high costs to projects.

The molecule complexity impacts stability, polymorphism, flow characteristics, solubility/bioavailability and particle size distribution, and variations in conditions (like ones encountered when moving from small-batch development to large-scale manufacturing) can lead to a large variety of deviations.

Being organized and detailed when it comes to complex molecules can help identify potential problems to avoid them altogether or have options in place if issues do arise.



It is important to characterize the physical properties that are critical to formulation and the intended drug product, identify the characteristics of target API for large-scale production, adjust the API process to achieve the desired characteristics and determine the characteristics of the target API for use in future production. This can help identify potential problems—such as a change in product behavior during the purification process due to a longer residence time—to avoid them altogether or have options in place if issues do arise.



Chapter III:

Why Phase-Appropriate Formulation Is Important

Phase-specific formulation and process design changes reduce risk at every stage, leading to **more success at each step of the development process**.

At the formulation design stage, using a QbD (quality by design) approach is crucial to reduce the number of iterations and project risks. QbD helps companies identify and correct the root causes of problems earlier in the design phase, which leads to higher quality and a lower risk of yield and supply chain issues.

Using a **QbD (quality by design) approach** is crucial at the formulation design stage to reduce the number of iterations and project risks.

With data gathered from QbD, companies gain intimate knowledge of the drug substance from its physiochemical properties to characterization and raw material and excipient reactions. This helps researchers develop a target product profile, understand what is needed for dosage form design, as well as what to expect for shelf-life stability.

In Phase II development, researchers evaluate the scalability of manufacturing processes and the potential regulatory impact of any changes. In Phase III, performance standards tighten with a formulation focus on reducing variability.



Chapter IV:

Why Communication & Collaboration Are Important

A team that is working toward the big picture, a common goal—the same finish line—is one that is in lockstep alignment and working together to get the new drug molecule to market. That can only happen if everyone knows what is going on and what is expected of them, which is where good communication and collaboration come in.

A major hurdle in developing a new drug lies in aligning the timeline for drug substance manufacturing with the drug product formulation. Typically, chemists and engineers have completed the development of the drug substance manufacturing process when final commercial formulation begins. Unfortunately, the separation in processes can lead to gaps in knowledge about drug substance properties which can lead to formulation development problems. This is also where the investment in molecule characterization pays off through critical knowledge that can lead to fewer headaches and rework in formulations.

A team that is working toward the big picture, a common goal—the same finish line—is one that is in lockstep alignment and working together to get the new drug molecule to market.



Why Communication & Collaboration Are Important

Why Choose Ascendia Pharma for Drug Formulation Development

[Ascendia Pharmaceuticals](#) is a specialty pharmaceutical company dedicated to developing enhanced formulations of existing drug products and enabling formulations for pre-clinical and clinical stage drug candidates. Ascendia provides state-of-the-art formulation development services for poorly water-soluble molecules and cGMP manufacturing of clinical trial materials. Applying its [nano-particle technologies](#) and expertise, Ascendia can rapidly assess the feasibility of a broad array of formulation options to improve a drug's bioavailability. Our technologies include nano-emulsions, amorphous solid dispersions, oral controlled release, self-emulsifying drug delivery systems (SEDDs) and production of nanoparticles. [Ascendia provides development and testing services](#) – from pre-formulation to manufacture of pilot clinical supplies.

We execute rapid, comprehensive and cost-effective programs for our clients. We partner with emerging, discovery-stage pharmaceutical companies to provide early-stage formulations; with generic companies that seek enabling technology for ANDA development projects; and with specialty pharmaceutical companies that need development of new 505(b)(2) products for clinical testing.

[Ascendia's headquarters](#), laboratories and manufacturing suites are in central New Jersey, and the company also has a facility in Xiamen, China to serve formulation development needs of the Chinese market. Ascendia is a privately held company with a mission to provide customized formulation solutions to salvage difficult compounds and to create advanced medicines to help patients prevail over their disease and enhance their quality of life.

Contact Us

We're ready to hit the ground running.

Contact Us



Ascendia Pharmaceuticals provides rapid, comprehensive, and cost-effective solutions for difficult formulation development projects, as well as the cGMP manufacture of clinical trial materials. [Contact us today](#) to learn more.

References

Deore, AB, Dhumane JR, Wagh HV, Sonawane RB, The Stages of Drug Discovery and Development Process. Asian Journal of Pharmaceutical Research and Development. 2019; 7(6):62-67, DOI: <http://dx.doi.org/10.22270/ajprd.v7i6.616>

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