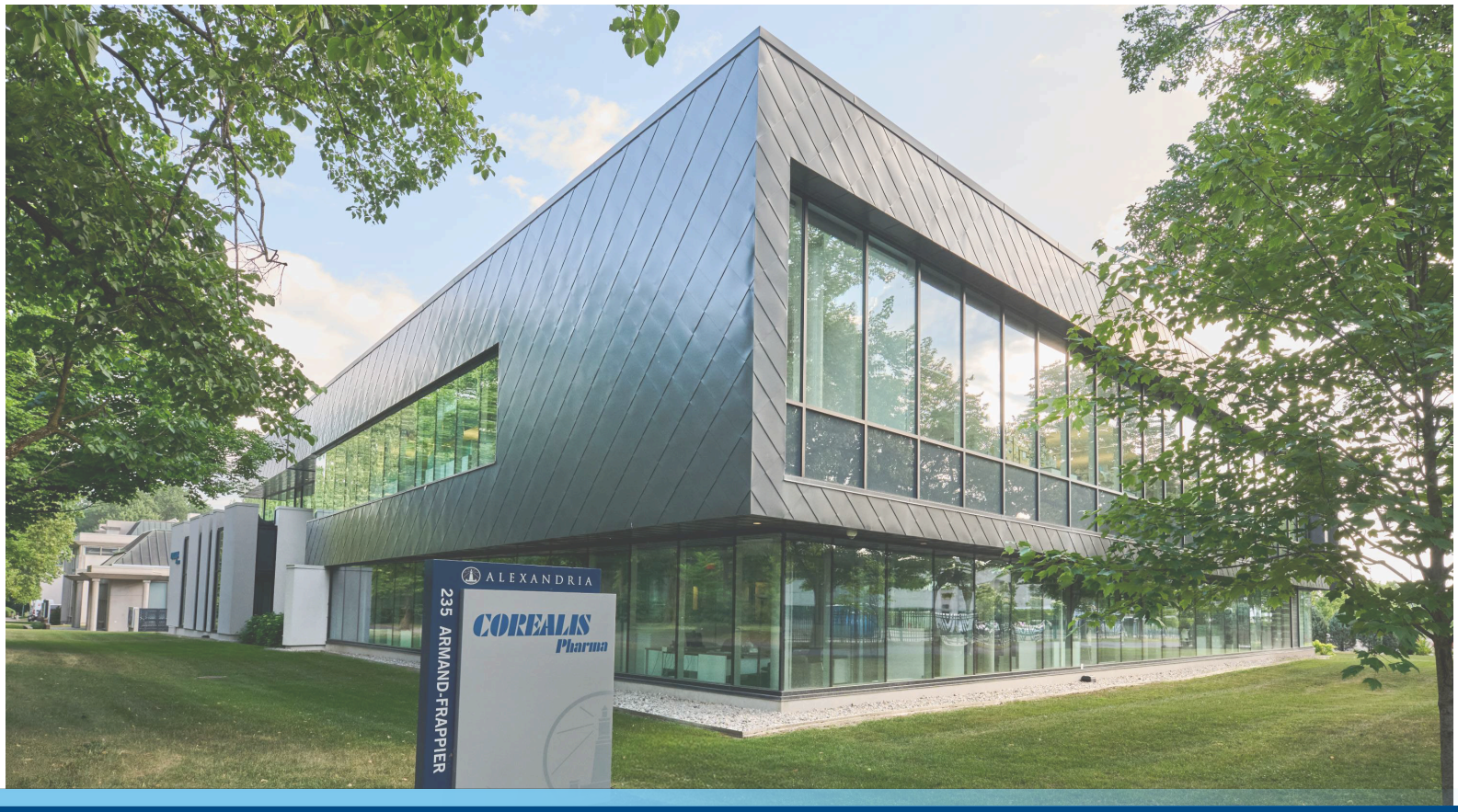
Reducing Development Risk
- Guideline



COREALIS
Pharma

Executive Overview

Drug product development is a complex, resource-intensive process with high attrition rates and significant regulatory requirements. Success depends not only on therapeutic innovation but also on early identification and mitigation of scientific, technical, and manufacturing risks. Industry analyses indicate that nearly 90% of investigational programs fail before approval, often for reasons that could have been identified earlier.

Corealis Pharma has honed the process of reducing risk by applying a structured, science-driven framework spanning pre-formulation through clinical supply manufacturing. By integrating physicochemical characterization, formulation science, and scalable process design, this approach supports informed decision-making, accelerates timelines and reduces development uncertainty.

Risk as a Determining Factor in Development **Success**

Clinical attrition remains a defining challenge. Principal causes of failure are primarily due to:

- **40-50% insufficient clinical efficacy**
- **30% unmanageable toxicity**
- **10-15% poor drug-like properties**
- **10% poor strategic planning or lack of commercial viability**

Many of these issues originate early in development rather than during clinical testing itself. When such limitations are discovered late, remediation can require reformulation, additional studies, or program termination. Early-stage evaluation is therefore a critical strategy for improving efficiency and reducing downstream risk.

Selecting the Most Appropriate **Active Pharmaceutical Ingredient (API)**

Selecting an appropriate active pharmaceutical ingredient (API) is foundational. Beyond pharmacological activity, a viable API must be manufacturable, stable, scalable, and suitable for patient use.

Key parameters evaluated during feasibility assessment include:

- Solubility and dissolution
- Chemical and physical stability
- Permeability
- API–excipient compatibility
- Particle size and distribution
- Solid-state characteristics, including polymorphism

Systematic evaluation of these attributes enables early identification of development risks and supports proactive formulation design.

Influence of **Particle Properties**

Particle characteristics strongly influence both manufacturing performance and therapeutic behavior.

/ PARTICLE SIZE

Smaller particles typically dissolve faster, improving absorption potential.

/ PARTICLE SHAPE

Morphology affects powder flow, compressibility, and packing behavior. Spherical particles generally flow more predictably than irregular shapes.

/ PARTICLE SIZE DISTRIBUTION

Narrow distributions promote batch consistency, reduce aggregation, and improve dose uniformity.

Careful characterization and optimization of these properties enhance both product performance and process reliability.

/ Addressing Suboptimal API Characteristics

Drug substances do not always exhibit ideal physical or chemical properties. However, limitations in particle morphology or distribution do not necessarily preclude development. Early technical intervention can mitigate such challenges through methods including:

- Micronization
- Crystal engineering
- Spray drying
- Wet or dry granulation
- Geometric dilution

These approaches demonstrate that formulation strategy can significantly influence a molecule's development viability.

Additional **Determinants** of Drug **Substance Suitability**

/ Permeability

Permeability is a key determinant of oral bioavailability. Although high permeability is advantageous, low permeability can often be addressed through formulation technologies or excipient systems that enhance absorption.

Excipients—while pharmacologically inactive—play critical roles in manufacturability, stability, release characteristics, and patient usability.

/ Solubility and Drug Dissolution

Limited solubility is a common barrier to effective drug delivery. Dissolution profiles, particularly those influenced by pH, determine absorption location and extent. Appropriate formulation strategies can significantly enhance solubility and bioavailability.

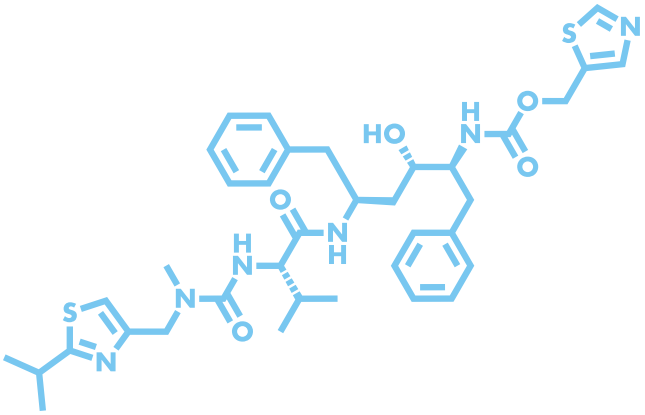
/ MODIFYING ABSORPTION PROFILES

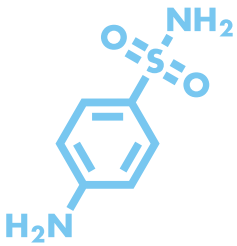
Technologies such as amorphous solid dispersions produced via spray drying or hot-melt extrusion are frequently used to improve solubility of poorly soluble compounds. Stability considerations associated with such systems can often be managed through optimized formulation and packaging.

/ Polymorphism

Polymorphism refers to the ability of a substance to exist in more than one crystalline form.

Polymorphic forms may differ in melting point, dissolution rate, and stability. Some forms may convert over time, potentially affecting product performance. Early characterization and control of polymorphism are therefore essential.





/ RITONAVIR DRUG DEVELOPMENT JOURNEY

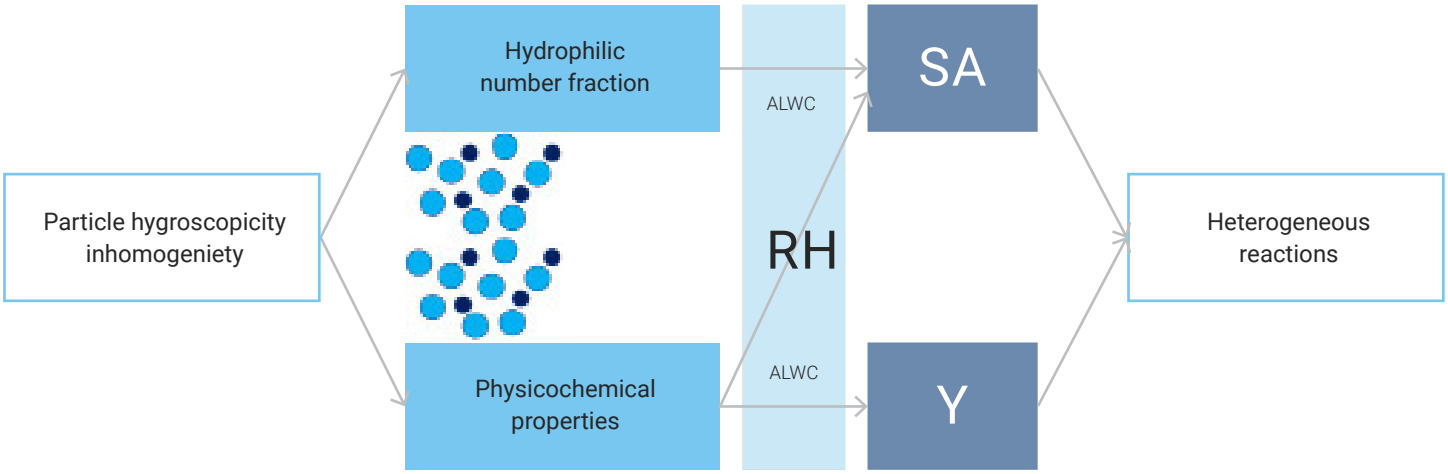
One notable example of how a polymorphic API complicated a drug development journey is Ritonavir (Norvir) — an antiretroviral drug used to treat HIV/AIDS. The API has at least two polymorphic forms. It was initially developed and marketed in one form, but during manufacturing, the API converted to a more stable (but less soluble) form, which adversely impacted bioavailability. The unanticipated polymorphism required the drug product to be reformulated.

/ SULFANILAMIDE AND THE "ELIXIR DISASTER OF 1937"

Sulfanilamide — a common antibiotic — can take many polymorphic forms, each with varying dissolution rates. While some forms dissolve too slowly, others are absorbed too quickly and can cause unpleasant side effects. The unfortunate outcome in this case wasn't directly related to the polymorphism of sulfanilamide, but it influenced how its polymorphic nature was carefully controlled in later formulations. It's also a textbook example of formulation gone terribly wrong: It was originally dissolved in a toxic solvent (diethylene glycol) and distributed in the US, killing over 100 people.

/ Thermal and Environmental Considerations

Thermal properties influence process design, storage conditions, and stability. APIs with low melting points require carefully controlled processing to prevent degradation. Hygroscopic materials may absorb moisture and undergo structural or chemical changes. Understanding these attributes early supports appropriate formulation and packaging decisions.



/ Hygroscopicity

Hygroscopicity refers to the drug substance's ability to absorb moisture from the environment. When exposed to humidity, an extremely hygroscopic API may undergo changes to its physical and chemical properties. While a skilled CDMO may be able to find solutions to address hygroscopicity, ultimately, successful commercial manufacturing in large facilities may still be achievable with extensive and costly strict humidity controls.

/ THE CASE OF THE MORPHING API

We were once sent a drug substance to evaluate, and as soon as we opened the jar, the API took on 15% of its weight in water within 24 hours. As it turns out, the API in question was an HCl salt. Our readers with a background in chemistry can predict what happened next. When added to water, HCl salts form hydrochloric acid.

/ Attributes of an Optimal Drug Substance

An API well suited for development typically exhibits:

- Favorable particle morphology and distribution
- Appropriate solubility and dissolution characteristics
- Adequate permeability and stability
- Controlled polymorphic behavior
- Suitable thermal properties
- Limited hygroscopicity

Alignment of these attributes supports predictable processing and consistent therapeutic performance.

Integrating **Innovation**, **Scalability**, and **Cost**

Early physicochemical assessment provides essential insight into development feasibility and informs strategic planning.

/ Excipients and Delivery Technologies

Drug delivery systems can regulate release profiles and optimize therapeutic performance. Excipients may improve stability, enhance bioavailability, and influence patient acceptability through sensory characteristics. As a rule, Corealis drug formulators will often deliberately avoid proprietary excipients unless there is a very strong technical justification, because they introduce regulatory, supply-chain, cost, and lifecycle risks that can outweigh their benefits—especially in early and mid-stage development.

/ Manufacturing Strategy and Scalability

Process decisions made during early development strongly affect scalability and cost efficiency. Selecting appropriate manufacturing technologies at the outset reduces risk during scale-up and later development stages.

/ Risks of Incomplete Evaluation

Insufficient early characterization increases the likelihood of failure in initial clinical studies, such as single ascending dose or multiple ascending dose trials. Thorough assessment prior to clinical entry is therefore essential.

/ Key to Phase I Drug Substance Success

For Phase 1 clinical development, direct compression or simple powder-in-capsule formulations are generally not recommended because they bypass the systematic understanding of the drug substance's physicochemical, solid-state, and biopharmaceutical properties. While fast to execute, these "place-and-pray" approaches often mask critical issues such as poor flow, content uniformity risk, excipient incompatibility, moisture sensitivity, and dissolution variability—problems that frequently emerge later and force reformulation, repeat stability, or clinical bridging. In contrast, a complete preformulation and rational formulation program establishes control over solid form, particle attributes, stability, and in vivo performance early, resulting in a Phase 1 drug product that is more robust, scalable, regulator-defensible, and far less likely to derail development timelines downstream.

/ Evaluation of Phase I Candidate Formulations

Before clinical testing, candidate formulations are evaluated using multiple performance criteria:

- **Appearance and physical integrity**
- **Mechanical strength and friability**
- **Powder flow properties**
- **Dissolution performance**
- **Content uniformity**
- **Stability under environmental stress**
- **Pharmacokinetics in preclinical models**

These assessments ensure that only well-characterized formulations advance to first-in-human studies.

8 Steps to Producing **High-Quality**, Early-Phase **Clinical Trial** Materials

After identifying a promising prototype (or several prototypes), the following steps should be considered:

1. **Manufacturing optimized prototype batches**
2. **Confirming process reproducibility with demonstration batch**
3. **Conducting biorelevant dissolution studies**
4. **Performing stability testing**
5. **Selecting optimal formulation based on pharmacokinetic data**
6. **Scaling manufacturing processes**
7. **Validating analytical methods and release testing**
8. **Packaging and distributing clinical trial materials**

This structured progression, that Corealis initiates, supports product consistency, regulatory readiness, and reliable clinical performance.

Conclusion

High attrition rates in drug development highlight the importance of early technical evaluation and risk mitigation. Identifying limitations during pre-formulation and formulation stages enables proactive resolution, reducing the likelihood of costly delays or late-stage failure.

Corealis Pharma has proven a systematic, science-driven approach integrating physicochemical characterization, formulation expertise, and scalable manufacturing design supports more efficient development pathways and increases the probability of clinical and commercial success.

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