

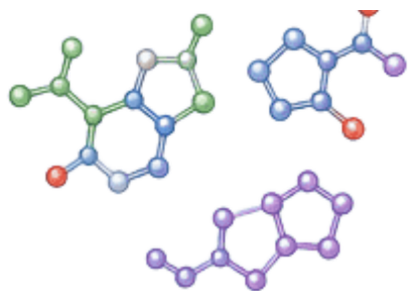
Early Development Approaches to De-Risk Complex Oral Solid Dosage Formulations

Introduction

Small-molecule drug development is becoming increasingly complex. Highly targeted and potent therapeutics, poorly soluble compounds, increasingly sophisticated drug delivery technologies, and accelerated clinical timelines are creating new challenges for pharmaceutical and biotechnology companies developing oral solid dosage (OSD) products.

For emerging and development-stage biotechnology companies in particular, access to specialized formulation expertise, fit-for purpose equipment, analytical capabilities, and GMP clinical manufacturing infrastructure can be critical to moving efficiently from API to clinic.

As a specialized contract development and manufacturing organization (CDMO) focused on oral solid dosage forms, Corealis Pharma supports drug development programs from pre-formulation and formulation development through process optimization, GMP clinical trial manufacturing, packaging, stability, and technology transfer to commercial manufacturing partners.



Early development decisions have consequences far beyond the first clinical batch. Formulation and process strategies must ultimately support reproducibility, scalability, stability, manufacturability, and regulatory expectations. Incorporating these considerations early can significantly reduce downstream development risk and help sponsors avoid costly reformulation, process redesign, or delays during clinical development and subsequent scale-up.

Speed Matters in Early Development

For biotechnology companies, development timelines often have significant financial and strategic implications. Reaching clinical milestones faster may influence financing, partnering, valuation, and overall program viability.

Corealis' integrated structure is designed to reduce handoffs among multiple external providers and allow formulation, analytical, process-development, stability, manufacturing, and packaging activities to be coordinated within a unified program.

Depending on API readiness, program complexity, analytical requirements, and formulation strategy, Corealis can potentially progress from API receipt to an IND-ready formulation in approximately 6-8 weeks for appropriately scoped programs.

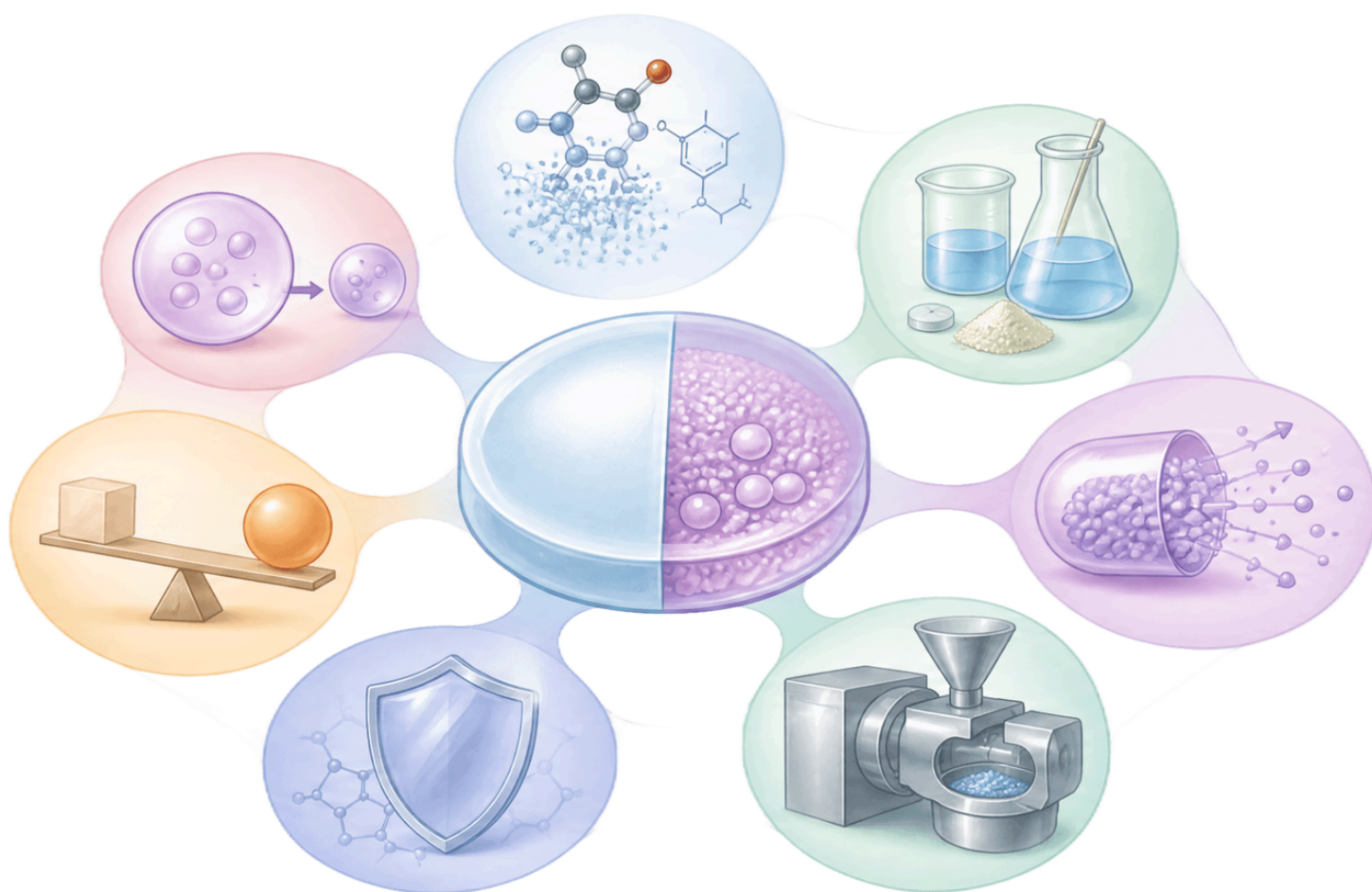
The objective is not simply speed. The objective is scientifically informed speed—moving efficiently while generating sufficient formulation and process understanding to reduce downstream risk.

Defining Complexity in OSD Development

Complexity in small-molecule OSD development can arise from many sources, including the physicochemical properties of the API, formulation technology, dose, potency, desired release profile, manufacturing process, stability requirements, and interactions among these factors.

A compound that appears relatively straightforward during discovery may become considerably more challenging when translated into a robust and scalable drug product.

At Corealis, development strategies are therefore built around understanding the molecule, formulation, analytical requirements, and manufacturing process as an integrated system rather than as independent activities.

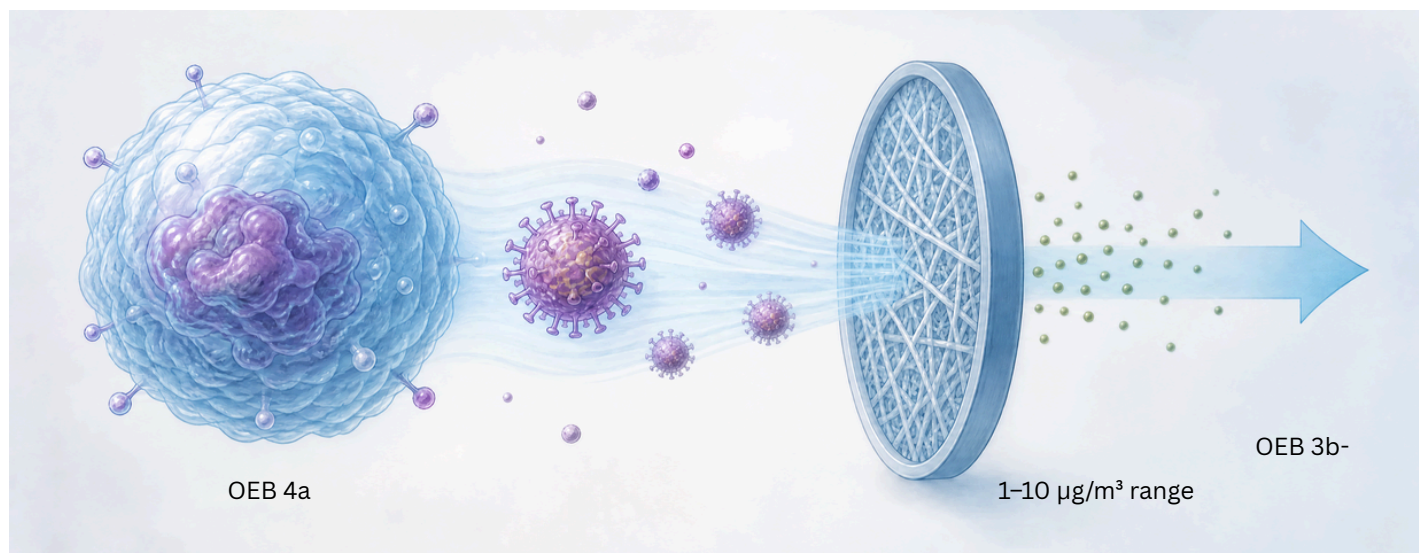


Highly Potent APIs

Increasingly potent drug candidates require specialized handling strategies and careful consideration throughout formulation development and manufacturing.

Because highly potent APIs can produce biological effects at very low exposure levels, appropriate containment is critical to protecting personnel and preventing cross-contamination.

Corealis has established containment capabilities supporting compounds up to OEB 3b-4a, with occupational exposure targets in the approximately 1–10 $\mu\text{g}/\text{m}^3$ range, subject to compound-specific safety assessment.



Containment considerations are incorporated into the development strategy from the beginning of a program and may include appropriate engineering controls, material handling procedures, cleaning strategies, personnel protection, and production workflows.

Potent compounds can also introduce important formulation challenges. Low-dose products, for example, require particularly robust approaches to blend uniformity and content uniformity. Understanding the impact of particle size, excipient selection, blending, granulation, compression, and other processing parameters can therefore be critical to achieving consistent product performance.

Solubility and Bioavailability Enhancement

Poor aqueous solubility remains one of the most common challenges encountered in small-molecule drug development.

For poorly soluble APIs, conventional formulation approaches may not provide sufficient dissolution or bioavailability. Sponsors may therefore need to evaluate enabling technologies early in development.

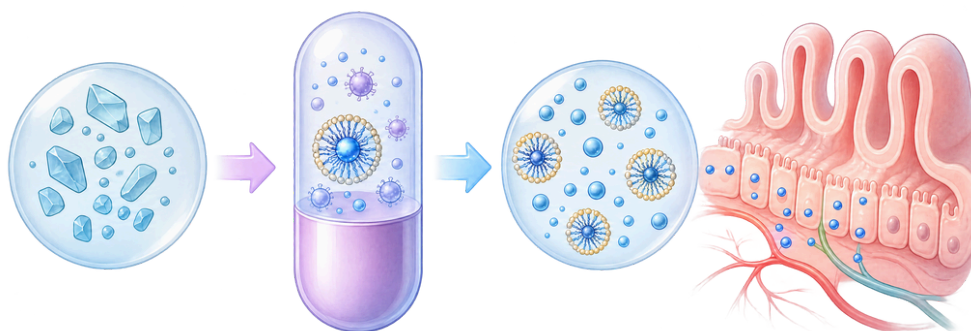
Corealis provides formulation development capabilities supporting several approaches to improve drug solubility and product performance, including:

- Amorphous solid dispersion development
- Spray drying
- Hot-melt extrusion
- Particle-size optimization
- Lipid-based formulation approaches
- Excipient and polymer screening
- Dissolution optimization
- Appropriate downstream processing into tablets or capsules



These technologies can significantly improve drug performance but also introduce additional development considerations.

Amorphous materials, for example, can be sensitive to temperature, humidity, processing conditions, and storage. Polymer selection, drug loading, residual crystallinity, moisture uptake, physical stability, and downstream manufacturability must therefore be evaluated together rather than independently.



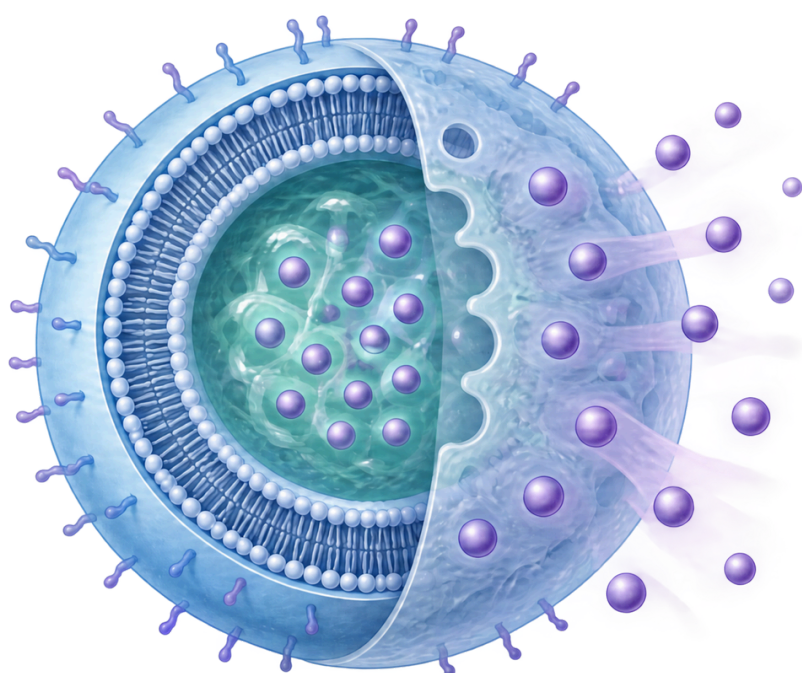
Corealis integrates formulation development with solid-state characterization and analytical testing using capabilities that can include XRPD, DSC/TGA, DVS, particle-size analysis, microscopy, dissolution testing, chromatographic analysis, and stability studies.

This integrated approach allows formulation candidates to be evaluated not simply on initial performance, but also on their potential to become robust clinical products.

Modified-Release and Advanced Drug Delivery

Modified-release formulations can provide important therapeutic advantages but are often significantly more complex to develop than conventional immediate-release products.

Extended-release, delayed-release, controlled-release, enteric-delivery, colon-targeted, and multiparticulate approaches require precise control of formulation composition and manufacturing parameters to achieve the desired drug-release profile.



Corealis supports development of advanced OSD approaches including:

- Extended-release formulations
- Delayed-release formulations
- Controlled-release matrix systems
- Functional polymer-based delivery
- Enteric and colon-targeted approaches
- Multiparticulate systems

Small changes in polymer level, particle size, compression force, granulation conditions, coating parameters, excipient functionality, or process conditions can significantly influence dissolution and overall product performance.

For this reason, Corealis integrates formulation screening with process development, dissolution method development, stability assessment, and manufacturability evaluation.

The objective is not simply to identify a formulation that works at laboratory scale, but rather to select one with a realistic path toward reproducible GMP manufacturing and subsequent scale-up.

Where Development Risk Emerges

Risk in complex OSD programs rarely comes from a single technical issue. It more often develops through the interaction of formulation, analytical, process, manufacturing, and program decisions over time.

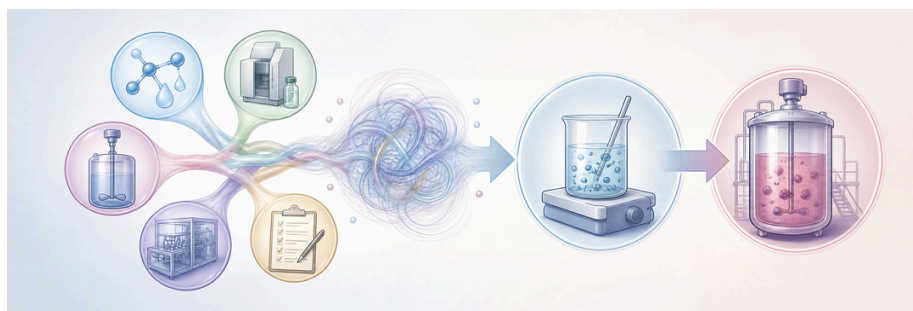
A formulation may demonstrate promising laboratory performance but subsequently become difficult to reproduce as batch size increases.

Likewise, modified-release formulations, amorphous solid dispersions, potent compounds, or moisture-sensitive products may be particularly sensitive to variations in:

- Raw material characteristics
- Particle size
- Mixing and granulation conditions
- Drying parameters
- Compression forces
- Environmental humidity

If these relationships are not understood early, problems may only become visible during engineering batches, GMP manufacturing, stability studies, or technology transfer.

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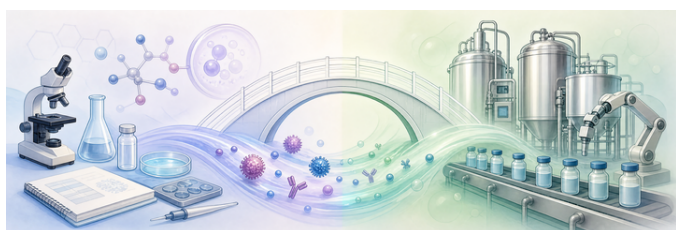
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Bridging Formulation Development and Manufacturing

One of the most important opportunities to reduce development risk is maintaining continuity between formulation development and clinical manufacturing.

Development programs can encounter difficulties when formulation scientists optimize a product without sufficient consideration for the manufacturing process that will ultimately be required.

Corealis was designed specifically around the integration of formulation development, analytical development, process development, scale-up, and GMP clinical manufacturing within the same organization and facilities. This allows scientists to consider manufacturability from the earliest stages of formulation development.



Processes can be evaluated at small scale using API-efficient equipment and progressively translated to larger development, engineering, and GMP scales.

Keeping development and clinical manufacturing closely connected provides shorter feedback loops between formulation scientists, analytical scientists, manufacturing personnel, quality teams, and project management.

This integration helps potential process limitations emerge earlier, when they are typically easier and less costly to address.

Specialized Capabilities for Complex OSD Development

Drug developers evaluating an OSD development partner should consider not only the technologies available, but also whether those technologies are appropriately scaled for the stage of development.

For early clinical programs, conserving API while generating meaningful process knowledge can be particularly important.

Corealis provides a broad range of development and clinical manufacturing capabilities specifically configured for small-molecule OSD programs.

Specialized Capabilities for Complex OSD Development

Advanced Formulation Technologies

- Immediate- and modified-release formulation development
- Hot-melt extrusion
- Spray drying
- Amorphous solid dispersion development
- Wet granulation
- Dry granulation
- Roller compaction
- Fluid-bed processing
- Tablet compression
- Capsule filling
- Film coating
- Multiparticulate and specialized oral delivery approaches
- Lipid-based formulation development
- Overencapsulation and clinical comparator preparation

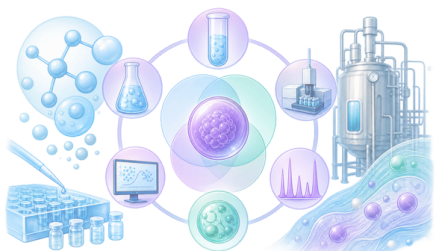


API-Efficient Development

Corealis maintains bench-scale and development-scale equipment that enables formulation scientists to begin development using relatively limited quantities of API.

Typical programs may begin with approximately 1-5g of API, depending on the molecule, analytical doses requirements, complexity, and development objectives.

This API-efficient approach is particularly valuable for emerging biotechnology companies whose drug substance may be costly or available only in limited quantities during early development.



Analytical and Solid-State Characterization

Corealis provides integrated analytical capabilities supporting formulation and process development, including:

- HPLC/UHPLC
- Dissolution testing
- XRPD
- DSC/TGA
- Dynamic vapor sorption
- Particle-size analysis
- Microscopy
- Bulk and tapped density
- Powder flow characterization
- Compression profiling
- Moisture analysis
- Stability studies under ICH conditions

Additional specialized analytical services can be coordinated externally when required.

GMP Clinical Manufacturing

Once a formulation and process have been selected, Corealis can support progression into engineering and GMP clinical manufacturing.

Corealis' Laval facilities contain approximately 60,000 ft² of laboratory, development, GMP manufacturing, packaging, stability, warehouse, and support space.

Manufacturing capabilities include 4 production modules and equipment suitable for development through clinical-scale manufacture.

Depending on the process and product, Corealis can support batch sizes ranging from approximately 1 kg to 250 kg.

Clinical manufacturing capabilities include:

- Blending
- Wet granulation
- Dry granulation
- Roller compaction
- Fluid-bed processing
- Milling
- Clinical labeling and kit preparation
- Encapsulation
- Tableting
- Film coating
- Bottle packaging
- Blister packaging
- Pouch packaging

Corealis primarily supports clinical-stage drug product programs, typically through Phase I and Phase II and, where appropriate, early Phase III development activities.

Environmental and Containment Capabilities

Environmental conditions can materially influence the manufacturability and stability of sensitive drug products.



Corealis provides controlled manufacturing environments and can accommodate specialized environmental requirements where technically feasible, including relative humidity conditions below approximately 20% RH.

Potent compounds are evaluated through a formal safety assessment before entering the facility, allowing appropriate containment and manufacturing strategies to be established before development begins.

Corealis' containment infrastructure supports compounds up to OEB3b -4a [1-10 µg/m³ range], subject to the compound-specific occupational exposure and safety assessment.

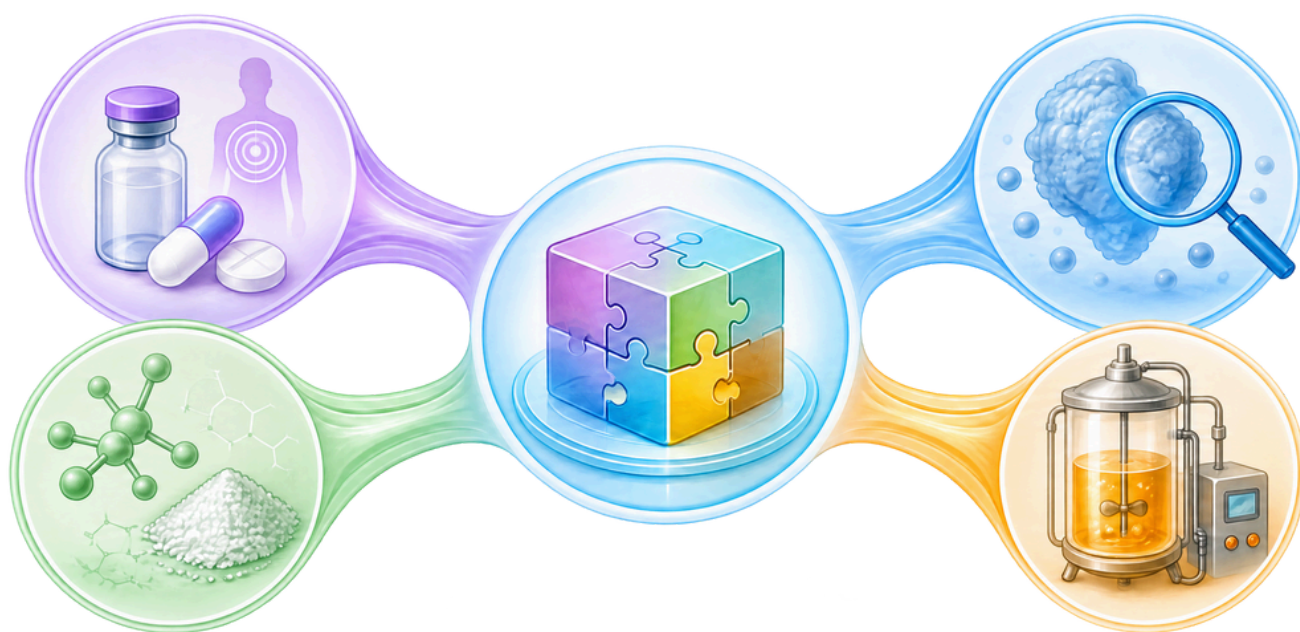
Building Scalability into Early Development

The objective of early formulation development should extend beyond producing material for the next clinical milestone.

Where possible, development should generate an increasingly robust understanding of the relationships between the formulation, raw materials, process parameters, equipment, and final product performance.

A Quality-by-Design-oriented approach can help identify:

- Quality Target Product Profiles (QTPPs)
- Critical Quality Attributes (CQAs)
- Critical Material Attributes (CMAs)
- Critical Process Parameters (CPPs)



Understanding these relationships helps establish appropriate process ranges and provides a stronger foundation for future scale-up and technology transfer.

For development-stage biotechnology companies, this can be particularly valuable because clinical success may ultimately require transfer of the drug product process to a larger commercial manufacturing organization.

How Integrated Development Capabilities Reduce Risk

For development-stage drug programs, the question is not simply whether a CDMO can manufacture a clinical batch.

Sponsors should evaluate whether their development partner can help establish the scientific and process understanding required to advance the program successfully.

At Corealis, formulation scientists, analytical scientists, process-development specialists, manufacturing personnel, quality professionals, and project managers work within an integrated organization.

This structure enables decisions made during formulation development to be rapidly evaluated against analytical results and real manufacturing constraints.

For example, a promising formulation identified during small-scale screening can progress through increasing levels of process development using equipment and manufacturing principles selected with eventual scale-up in mind.

Engineering batches can then provide additional process understanding before the program proceeds into GMP manufacturing.

The resulting knowledge package can become an important component of subsequent technology transfer to a commercial manufacturing partner.

Designing for Technology Transfer

Corealis' role does not end with production of clinical material.

A critical objective of development is establishing a formulation and manufacturing process that can ultimately be transferred successfully to larger-scale manufacturing.

Corealis has extensive experience transferring processes to pharmaceutical companies and commercial CDMOs.

Technology-transfer activities can include:

- Formulation and process documentation
- Manufacturing instructions
- Identification of critical process parameters
- Analytical method transfer
- Equipment comparison
- Scale-up assessment
- Technical discussions with receiving sites
- Support during engineering or demonstration batches
- Troubleshooting during transfer

Where appropriate, Corealis can also work collaboratively with established commercial manufacturing partners to provide continuity as products advance toward later-stage and commercial production. Through strategic alliances with Bora Pharmaceuticals and Rottendorf Pharma, Corealis can support a seamless transition from development to commercial manufacturing.

This development-to-commercial bridge allows sponsors to benefit from Corealis' specialized early-stage development expertise without requiring the early clinical process to remain tied to a single commercial manufacturing facility.

De-Risking as a Development Strategy

Increasing molecular complexity, poor solubility, potent APIs, specialized release profiles, and compressed development timelines have made OSD development more technically demanding than ever.

Formulations that demonstrate excellent laboratory performance may fail to translate successfully into reproducible manufacturing processes if scalability and manufacturability are not considered early. Successful programs therefore require more than access to individual pieces of equipment. They require coordinated formulation science, analytical development, process understanding, manufacturing expertise, quality oversight, and effective project management.

Corealis Pharma provides these capabilities within an organization specifically focused on small-molecule oral solid dosage development and GMP clinical manufacturing. By integrating pre-formulation, formulation development, analytical development, process optimization, clinical manufacturing, packaging, stability, and technology-transfer support, Corealis helps sponsors identify and address development risks while they are still manageable.

The result is a stronger foundation for clinical development and a more efficient transition toward future commercial manufacturing. For emerging biotechnology companies in particular, this approach allows precious API and capital to be deployed where they matter most: building a robust, scalable drug product and advancing it efficiently toward the clinic.

About Corealis Pharma

More than 21 years focused on pharmaceutical development

Corealis has specialized in small-molecule oral solid dosage development for more than 21 years, supporting biotechnology and pharmaceutical companies from early development through clinical manufacturing and technology transfer.

Approximately 60,000 ft² of specialized facilities

Corealis operates approximately 60,000 ft² of laboratory, development, GMP manufacturing, packaging, warehouse, and support space across its Laval facilities.

Dedicated formulation and analytical development teams

Integrated formulation, analytical, process development, manufacturing, quality, and project-management teams allow programs to progress within a coordinated development environment.

Potent compound capability

Containment capabilities support compounds through OEB3b -4a [1–10 µg/m³ range], subject to program-specific safety assessment.

Integrated analytical support

A comprehensive analytical platform enables characterization of API, formulations, intermediates, and finished drug products throughout development.

Established technology-transfer experience

Corealis has successfully transferred numerous drug-product processes to pharmaceutical companies and commercial-scale CDMOs following clinical development.

Proven development experience

Over its history, Corealis has contributed to 1,000+ development programs, including products and assets subsequently acquired or advanced by leading pharmaceutical companies

Broad OSD technology platform

Capabilities include:

- Tablets
- Capsules
- Modified-release products
- Amorphous solid dispersions
- Spray drying
- Hot-melt extrusion
- Wet and dry granulation
- Roller compaction
- Fluid-bed processing
- Functional coating
- Multiparticulates
- Lipid-based approaches
- Overencapsulation

Clinical-scale manufacturing

Corealis supports development and GMP manufacturing from small laboratory batches through approximately 250 kg, depending on product and process requirements.