Oral solid dose

Reducing uncertainty in early oral drug development: Decisions that benefit from predictive insights

Why early development requires a different decision model

Early oral drug development is an exercise in working under constraint. Teams are asked to make consequential decisions when materials are limited, timelines are tight, and the data are incomplete. Traditionally, formulation development has relied on empirical, sequential experimentation. While this approach remains essential, it can be costly in early development. When issues with solubility, permeability, or bioavailability arise, repeated reiterations can quickly consume limited API and valuable time.

This shift is fueled by a rapidly growing industry interest in digital tools. Beyond simply saving time, there is a rising recognition that digital tools, specifically ones that use AI and ML, provide a level of predictive certainty that physical trials simply cannot match in terms of time and costs at this stage. Modern drug developers are increasingly looking to AI-driven models not as a replacement for the lab, but as a strategic necessity to justify early-stage capital investment and navigate complex regulatory pathways with data-driven confidence.

A different decision model is gaining traction in early development. Predictive formulation insights allow teams to narrow their empirical work on what is most likely to succeed, improving development efficiency without replacing experimental science. Using AI in early drug development help narrow experimental paths and reduce unproductive trails to preserve scarce API, accelerate learning, and generate data that support confident discussions with regulators and investors. Importantly, this early development phase forms the foundation of how customers demonstrate asset visibility through clear scientific rationale, more reliable timelines, and more efficient use of limited materials.

Five early decisions that shape oral drug development

When there is immense pressure to progress with limited API and data, these five early decision points can significantly influence downstream success. Across early development, five decision points recur, and each represents an opportunity to reduce uncertainty with early insight.

1. Choosing the right solubility enhancement strategy

As most drug candidates are hydrophobic, many enter development with intrinsic solubility or permeability challenges, if left unaddressed, represent a primary reason for clinical trials to fail due to poor bioavailability. Over 50% of IND failures occur due to poorly characterized drug substance, leading to delayed trials, formulation challenges, and costly rework. Last-minute process changes can create CMC inconsistences, which can bring additional scrutiny from regulatory affairs. Teams must decide whether existing formulation strategies can realistically overcome these limitations, or whether molecular intervention is required upstream. Making this call too late can be a costly mistake, as early-stage inefficiencies account for up to 30% of total drug development costs caused by excessive screening, unnecessary API consumption, and slow convergence on a viable path.

Integrating predictive insights early in the development stage allows teams to prioritize specific excipient classes and formulation technologies. By selecting the most promising solubility-enhancing pathways before clinical trials begin, developers can ensure that the clinical formulation delivers the exposure levels necessary to meet therapeutic targets. Ultimately, a data-backed solubility strategy serves as a critical de-risking mechanism, mitigating the potential for clinical failure due to poor absorption and providing the scientific rationale required to maintain momentum in early development.

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2. Projecting dose and exposure for FIH readiness

Human dose and exposure estimates are required well before complete formulation or before in vivo datasets exist. These early projections influence clinical planning, API demand, and timelines, yet they are often made under significant uncertainty. Early modeling of absorption and exposure provides clarity that helps teams set realistic expectations for FIH studies, without consuming excessive API.

3. Identifying API–formulation compatibility and manufacturability risk

Not all APIs are compatible with all formulation approaches. Physical and chemical properties of APIs can introduce manufacturability risks, that may only surface after significant development effort. When incompatibilities are discovered late, teams are often forced to rework with even less time and materials. Lack of clinical efficacy account for 40–50% of clinical drug development failures, stemming from poor drug-excipient compatibility and stability issues.

Evaluating API–formulation compatibility early helps teams avoid committing scarce material to approaches that are unlikely to scale or transfer. Early risk identification supports more resilient development strategies from the outset.

4. Treating stability as a design constraint

Degradation behavior can strongly influence formulation choices, packaging, and storage assumptions. Waiting to obtain long-term data before adjusting strategy can lead to costly late-stage remediation. Over 40% of NDA delays are linked to stability-related issues, and the regulatory agencies are requiring comprehensive solid-state characterization upfront. Early insight relying on digital modelling into degradation pathways allows teams to treat stability as a design input rather than a validation step that happens too late. This approach enables smarter use of material and reduces the risk of unpleasant surprises downstream.

5. Anticipating scale-up and transfer feasibility

Formulation decisions made early can either simplify or complicate future scale-up and site transfer. To avoid downstream complexity when materials are constrained, teams are increasingly utilizing compaction simulation as a risk-mitigation strategy. Rather than wasting precious API performing large-scale experiments by trial and error, compaction simulations require only a few grams to model full-scale production. By mimicking the kinetics of commercial equipment at a lab scale, this technology allows for a data-driven approach that achieves “right-first-time” validation batches. Ultimately, this saves significant amounts of API and avoids unnecessary timeline delays.

What predictive insights look like in practice

Across early development programs, predictive insights are already informing early decisions under strict API constraints. To help sponsors navigate these early challenges, Thermo Fisher Scientific developed OSDPredict™ platform, a comprehensive digital toolbox powered by AI/ML designed to solve formulation challenges before they cause issues downstream. By combining multiple predictive models like proprietary Quadrant 2™ algorithms, OSDPredict platform can deliver data-driven foresight into solubility, bioavailability, FIH dosing, and scale-up planning, often before a single batch is produced.

Across development programs, the OSDPredict platform helped to solve 400+ solubility issues since 2011. Below are two examples of how the OSDPredict digital toolbox has been used to de-risk early development.

Case study 1: Structure-based solubility enhancement

The challenge: A client came with a drug compound with very poor solubility that demonstrated limited bioavailability and clinical success. Initially, the client proposed an extensive experimental plan involving multiple technologies and excipients, which would have required significant time, cost, and API.

The approach: By using Quadrant 2 algorithms, the team utilized AI/ML and molecular dynamics simulations to screen excipients and optimize drug loading. This narrowed the selection for screening *in silico*.

The results: The algorithm achieved >90% prediction accuracy, identifying specific lead polymers (PVAP and HPMCAS-M), that were then validated in animal PK studies. This led to a clinical trial formulation showing a near 8-fold enhancement in C_{max} and ~5-fold enhancement in AUC compared to the crystalline drug. This enabled the successful scale-up of their spray drying process, and led to rapid progression of Phase I clinical trials with significantly improved bioavailability.

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Case study 2: Compaction simulation for dual-sourcing risk mitigation

The challenge: A sponsor required a validation strategy at lab-scale to assess the impact of a dual API sourcing approach for a late-phase drug product. The goal was to validate the new API source under an accelerated timeline using a data-driven, risk-based control strategy.

The approach: The team implemented a comprehensive Quality by Design study of the mechanical properties of both the drug substance (DS) and drug product (DP) to de-risk the program. Using the latest compaction simulator and rotary press, they employed a scale-up approach with optimized testing to identify compression kinetics and select parameters for pilot-scale runs.

The results:

- Material saved: The study required only 45 grams of API for R&D trials, successfully saving 30 kilograms of expensive material.
- Timeline acceleration: The data-driven approach accelerated the validation finish by 3 months, reducing the overall time to market for the new API source.
- Technical certainty: The simulation confirmed the design space, de-risked scale-specific defects, and enabled “right-first-time” validation batches.

Why predictive insights are becoming integral to early development strategy

As expectations for capital efficiency and development predictability continue to rise, drug developers are expected to justify early decisions with defensible data. Tools like OSDPredict digital toolbox are providing predictive formulation insights that help make correct decisions early on, ensuring they are backed by scientific rigor. In an environment where early choices carry lasting consequences, predictive insights gained sooner can be the strategic advantage that accelerates clinical success and secures investor confidence.

Learn more about **OSDPredict**
or email us at **pharmaservices@thermofisher.com**

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