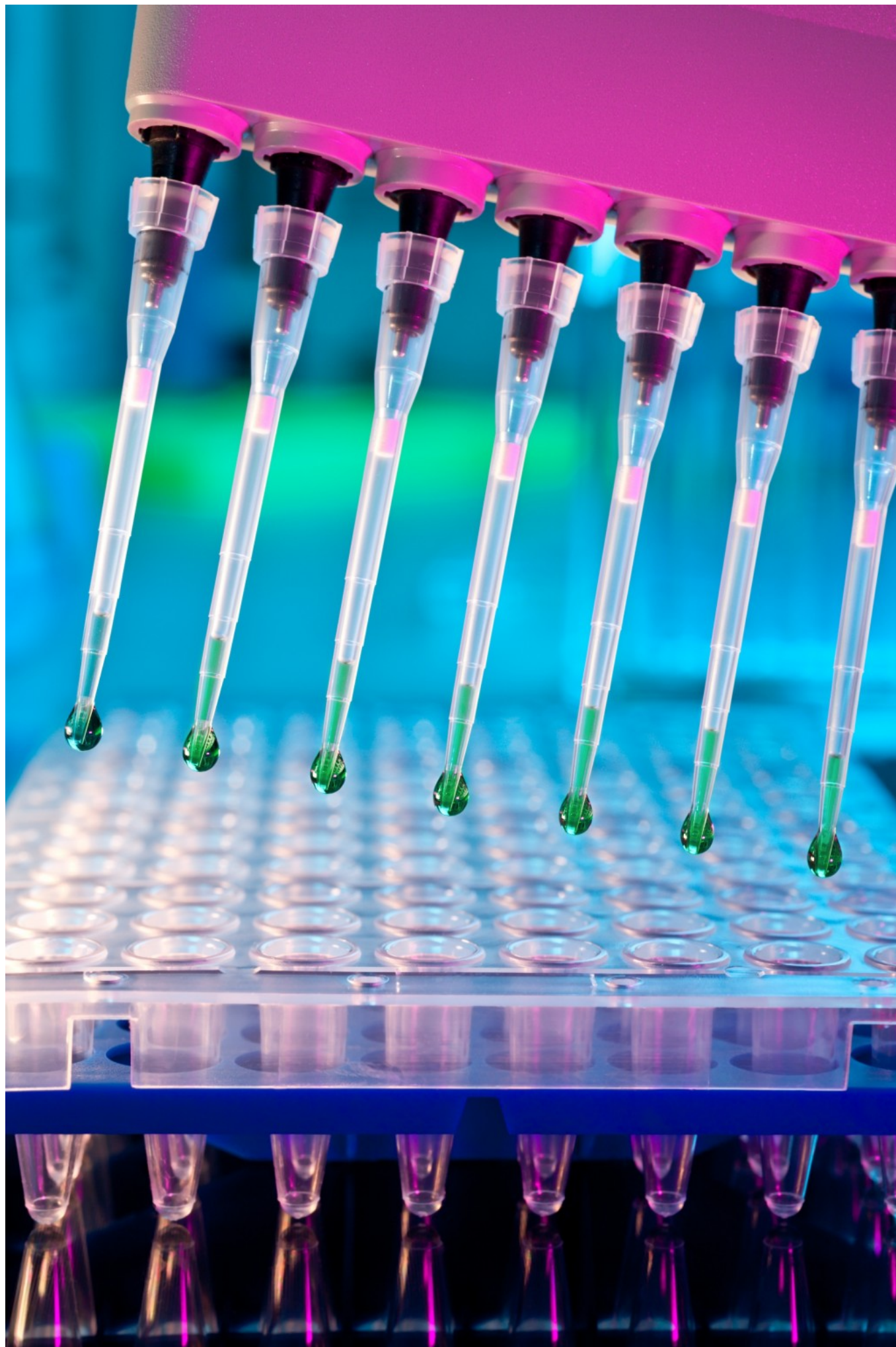


Why Do Promising Discovery-Stage Compounds Fail Later in Development and How CDMOs Can Help Reduce the Risk



San Diego, California Oct 10, 2026 ([IssueWire.com](http://www.IssueWire.com)) - Key takeaways

- **Potency alone is not enough for candidate selection.** Teams need to assess whether a compound can reach the relevant tissue, engage its target and produce the intended biological effect at tolerated exposures.
- **Earlier development and manufacturing input can reveal liabilities while they can still be addressed.** Bringing DMPK, toxicology, analytical, formulation and process expertise into lead optimization helps teams make more informed decisions before candidate nomination.
- **Integration adds value when findings lead to coordinated action.** WuXi AppTec's molecular glue degrader and siRNA-lipid conjugate examples show how customized assays and redesigned synthesis routes can address specific hurdles and support progress toward IND submission.

A compound can look exceptional in an early assay and still be a poor development candidate. Potency against an isolated target answers an important question, but not the decisive one: Can the molecule produce the intended effect in the right human tissue at a tolerable exposure, in a form that can be manufactured consistently? Later failures often expose evidence gaps that were present, but unresolved, during discovery.

Teams can reduce this risk by testing the therapeutic hypothesis more rigorously, evaluating the whole candidate profile rather than potency alone and bringing development and manufacturing considerations into discovery before candidate selection.

At [WuXi AppTec](http://WuXiAppTec.com), medicinal chemistry programs increasingly bring biology, pharmacology, and DMPK/ADME data into these decisions earlier, because the sooner compound's weaknesses are understood, the more options there are to address them.

Why potency alone isn't enough for candidate selection

A compound's potency in a discovery assay does not establish whether it can achieve sufficient exposure at the site of action, produce the intended biological effect or maintain an acceptable safety margin. Tao Guo, Ph.D., senior vice president, Research Chemistry Services, Integrated Program Management at WuXi AppTec, has identified translatability as a central challenge in early discovery: compounds that perform well in biochemical assays may lose activity in cellular or in vivo systems. Factors such as cell permeability, target abundance, protein turnover and the surrounding tissue environment can influence how assay results translate into biological activity.

Candidate selection therefore requires a balanced assessment of multiple properties. Alongside potency and selectivity, teams should evaluate physicochemical properties, absorption, distribution, metabolism and excretion (ADME), and pharmacokinetics and pharmacodynamics (PK/PD). The key question is whether a compound can reach the relevant tissue at sufficient concentrations, engage its target and sustain the intended effect at exposures that are tolerated. Assessing these properties alongside off-target activity and early safety signals can help identify liabilities while there is still an opportunity to optimize the molecule.

The evidence supporting selection must also be reliable and relevant. Each experimental model should address a defined question, with its limitations understood. Models should be selected for their relevance to the mechanism of action, human disease biology and the intended clinical setting. No single model can establish clinical predictability, but integrating findings across complementary systems can reveal inconsistencies and strengthen the basis for candidate selection.

How earlier development and manufacturing input can reduce risk

Earlier development and manufacturing input can reduce risk by identifying formulation, analytical and scale-up liabilities while there is still an opportunity to address them through molecular design and lead optimization. A biologically promising molecule may be difficult to formulate, synthesize, purify or manufacture at scale. These challenges can be particularly demanding for structurally complex small molecules, targeted protein degraders, peptides, oligonucleotides and conjugates, each of which presents distinct requirements for solubility, stability, delivery, bioanalysis, purification and manufacturing.

Sequential handoffs from discovery to development and manufacturing can delay the assessment of these risks. By the time a downstream team identifies a liability, substantial resources may have been invested in the candidate. Bringing expertise in drug metabolism and pharmacokinetics (DMPK), toxicology, analytical chemistry, formulation, process chemistry and manufacturing into lead optimization can help teams address these liabilities before candidate nomination.

An integrated approach can translate an early target product profile into practical criteria for candidate selection, define the evidence required at each decision point and bring specialists together to assess conflicting findings. Less viable chemical series can be discontinued earlier, while promising candidates can be optimized with a clearer understanding of anticipated dose requirements, formulation options and manufacturing feasibility. Connecting these decisions early can reduce the likelihood that a discovery-stage success becomes a development bottleneck.

How integrated partners turn early findings into development decisions

An integrated partner can help reduce development risk by turning findings from individual disciplines into coordinated action. A bioanalytical gap may require a different way to measure biological activity, while poor synthetic efficiency may call for a new manufacturing route. CDMOs with connected research capabilities—or contract research, development and manufacturing organizations (CRDMOs)—can help teams address these problems while aligning the resulting changes with the broader development plan.

A molecular glue degrader program illustrates the importance of measuring the right biological effect. A customer sought WuXi AppTec's support because conventional target occupancy assays could not reliably show how much of the target protein was being degraded inside cells. This left gaps in the evidence needed to understand the compound's mechanism of action and guide dose selection. WuXi AppTec's Bioanalytical Services team developed a customized assay to measure intracellular target degradation by screening reagents, optimizing assay conditions and standardizing the testing workflow. The resulting data could be evaluated alongside DMPK findings to build a clearer picture of drug exposure and biological activity, supporting further IND-enabling development.

A separate siRNA-lipid conjugate program shows how changing a synthesis route can resolve several development challenges at once. The original route required customized lipid-functionalized support that took months to procure, while inefficient coupling reactions and difficult purification created additional

hurdles. WuXi TIDES redesigned the route so that the oligonucleotide was synthesized first and then conjugated to the lipid in solution. The revised process achieved conversion of up to 95% and reduced two purification steps to one. Lipid synthesis, analytical development, formulation and manufacturing progressed in parallel, allowing the required CMC activities to be completed within eight months to support IND submission.

These cases illustrate specific analytical and manufacturing hurdles that coordinated teams can address. They do not establish that integration alone improves clinical success rates. Its practical value lies in helping teams resolve avoidable liabilities, interpret evidence across disciplines and advance candidates with a more coherent development strategy.

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