

Can Early Development Strategies Avoid Later-Stage Disasters?

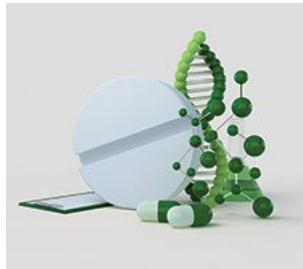
Assessing potential formulation and manufacturing issues in early development phases can improve a drug's chances for success.

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While some drug innovations are the result of surprises during research phases, a surprise that occurs during development—such as formulation or manufacturing problems—could result in approval delays or failure for a drug product.

To reduce the risk of late-phase surprises, some experts recommend that additional screening efforts in early development can smooth the pathway in later development stages. Developers of promising compounds emerging from drug discovery must balance the need to better understand potential formulation challenges and the manufacturability of the drug product with the reality of time and budget constraints.

For investigational new drug applications, drug owners are expected to provide information about the pharmacological and toxicological effects of a prospective drug product, as well as its physical, chemical, or biological characteristics and the stability of the drug substance during the toxicological studies and planned clinical studies. The application also requires information about inactive components planned for the drug product and “any reasonable variations that may be expected during the investigational stage” (1).

In the regulations, FDA notes that “modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses” (1). For a Phase I submission, drug companies should focus on the identification and control of raw materials and the new drug substance, the Code specifies; the agency does not expect final specifications for the drug substance and drug product until the end of the investigational process.

For drug development companies, particularly small startups, the focus is often short-term: get the compound to clinic or get an investor or buyer interested in the potential drug. This approach can be short-sighted, experts note, and drug companies would be better served by focusing on getting the drug to market. In presentations, consultants and representatives of contract development and manufacturing organizations (CDMOs) proposed that moving some formulation steps normally conducted in Phase I or Phase II to the preclinical stage can help identify potential formulation and manufacturability roadblocks earlier in the development process and avoid later problems.

Building a better molecule

While speed is the top priority for most small pharma companies with molecules in discovery phases, drug candidate quality should be the top consideration, said David Elder, principal consultant, David P. Elder Consultancy, in a webcast (2).

If more work is done in medicinal chemistry stages to optimize a molecule, formulation challenges may be easier to solve, said Elder. Historically, formulation scientists were expected to “rescue” molecules that were intrinsically insoluble. To get more drug candidates with fewer solubility issues, drug companies should focus more on the quality of the candidate molecule—its lipophilicity, molecular weight, and ring systems—and not just its potency.

Drug companies that fail to evaluate the physicochemical characteristics and manufacturability of a drug candidate in early development stages will not have adequate risk assessments of challenges that may arise later in development stages, experts agree. Drug candidates with demonstrated data on solubility, intestinal permeability, dissolution, bioavailability, and dose will be more attractive to potential partnerships, acquisitions by other pharma companies, or financing from investors.

Often, preclinical efforts are geared to achieving a desired pharmacokinetic response in an animal model while minimizing formulation development time and cost. However, *in vitro-in vivo* relationships are often not straightforward and, therefore, require additional time and cost to establish, experts note. Pharmacokinetic studies using the API in a hydroxypropyl methylcellulose suspension, may not give accurate results and can result in formulation delays later in the development process (3).

A range of *in-silico* modeling tools are available to screen drug candidates to predict degradation, metabolism, toxicity, solubility, and other characteristics, while conserving valuable API. Modeling also is used to evaluate manufacturing approaches and excipient selection, and for scale up and design of experiments.

The solubility question

As drug molecules become more complex, solubility has become a major hurdle in the development process. Drugs are frequently cited as fitting into one Biopharmaceutics Classification System (BCS) (4) classification; however, this system is a regulatory tool to identify efficacy and patient safety, said Julien Meissonnier, vice-president, science and technology, Catalent Pharma Solution, in a webcast (2). A better tool for evaluating new drug development issues including permeability, solubility, dose, and dissolution rate is the Developability Classification System (DCS) (5), he said.

Like the BCS, the DCS tool also categorizes molecules based on solubility, dose, dissolution, and permeability. It further classifies Class II compounds, which have low solubility and high permeability: Class IIa are dissolution-rate limited and Class IIb are solubility-limited. The dissolution of Class IIa molecules can be enhanced by reducing particle size. Knowing where a drug candidate fits on the classification scheme can expedite the formulation process, Meissonnier said.

Catalent works with drug companies to characterize a molecule using high-throughput screening to identify physicochemical properties and a DCS classification. Drug metabolism and pharmacokinetics modeling is used to understand formulation parameters. Parallel screening--at a small scale--of different solubility enhancing technologies (e.g., lipids, hot-melt extrusion, spray drying, and micronization) is used to assess stability, drug load, solubility, and concentration increase. Based on the screening results, the best candidate molecule can be selected for animal studies.

In a presentation (6), Sanjay Konagurthu, a senior director at Patheon, part of Thermo Fisher Scientific, described a solubility enhancement formulation platform that uses algorithms to analyze a drug's structure against manufacturing methods including solid dispersions, lipids, particle size reduction, crystalline forms, and cyclodextrin complexes. The results indicate the potential of each technology on a scale. The tools can be used to view a drug's molecular properties, identify potential excipients, and computationally screen excipients and drug loading prior to experimentation.

Build for the drug's lifecycle

In the typical drug discovery/early development scenario, a company may have only a few grams of the compound, and most likely has not attempted to synthesize the substance on a larger scale, or to formulate it to a drug product.

Changes in a formulation during process development can sidetrack a drug's development, and these potential risks are best assessed in early development stages, explained Jon Sutch, senior manager of formulation development, Patheon, in a webcast (7). Drug owners need to understand the risks involved with moving from one phase to another and how the formulation may change moving from process to process. Experimental work can mitigate some of the risk, he explained.

Drug owners should plan, in early development stages, to develop a synthesis platform that is sustainable--environmentally acceptable, socially acceptable, and profitable--throughout a drug's life cycle, said Peter Poehlauer, innovation manager, API, Patheon, in a webcast (8).

Initially, in Phase I and II clinical trials, a drug's API is expensive because there is so little material available; once the drug has reached Phase III trials, the API manufacturing process has been refined and the API cost drops, Poehlauer explained. While innovator drugs are expensive when launched, the API represents only 8-12% of the drug product cost. The cost of the drug product declines as it moves toward patent expiration; however, the API represents a greater percentage of the total drug cost.

For this reason, Poehlauer says, drug owners must develop the foundation for efficient, reliable, and scalable processes in the early clinical trial phases even before it is certain that the drug will succeed. An analysis of the original synthesis process for the compound may reveal alternate, more efficient methods required for large-scale production.

How much information is needed?

A challenge for drug owners in early development is balancing what they don't know, what they can afford to investigate, and what they need to know. A better understanding of an API's properties, polymorph forms, interactions with excipients, and the overall performance of the formulation can help avoid problems and expensive rework of formulation steps during scale up to commercialization.

For small pharma companies, limited financial resources may restrict their ability to conduct preclinical formulation screens. The added upfront costs may slow early phase development and increase costs, suggested FDA Commissioner Scott Gottlieb (see [Sidebar](#) [2]).

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Editor's note

Pharmaceutical Technology will host a panel discussion, Detecting Potential Formulation Roadblocks in Early Drug Development, on April 24, 2018 at CPhI North America. For details, see <http://cphinorthamerica.com> [3].

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