Leveraging knowledge about an API’s physicochemical properties from preformulation and formulation studies increases the chances of early-phase success.

Overview
Increasing the chances of success for early-phase development programs is a combination of how well experience, tools, processes, decision-making, risk assessment, risk tolerance, and company culture are leveraged to choose and develop viable candidates—drug substances (API) and drug products (formulations)—early in the program. To achieve success, scientists must design and develop high-quality candidates with the desirable and needed physicochemical properties; pharmacokinetic, pharmacodynamic, and metabolic profiles; structural motifs that minimize toxicity; and formulations that deliver the needed dose. But, what is the fastest pathway to success?

Pathways to Success: Culture and teamwork
In Producing Prosperity: Why America Needs a Manufacturing Renaissance, Harvard Business School professors Gary Pisano and Willy Shih, write, “innovation is not a laboratory discovery, a concept, or a prototype. Innovation is the process of taking a new idea or concept to the market….If this part of the innovation process fails, you don’t have an innovation; you had a promise.”

To successfully capitalize on these promises and quickly bring innovations to patients, it is critical that drug developers execute several elements related to planning, investment, and understanding of the risks, risk tolerance, and pitfalls inherent in the development program (see Figure 1). In addition, technical expertise, the CMC development-related narrative, and team dynamics and culture must come together within a fluid, rapidly changing, and complex development environment (see Figure 2). From a not necessarily linear continuum-of-development perspective, the development program should include priorities such as:

• quickly designing lead candidates with optimized physical forms, stability, biopharmaceutical and drug metabolism and pharmacokinetic (DMPK) characteristics, and minimal toxicity,
• reproducibly manufacturing and supplying the needed clinical supplies quickly,
• rapidly solving problems that surface,
• quickly assessing, measuring, and mitigating risk,
• speeding up, slowing down, stopping, and changing directions as needed; and
• understanding and incorporating the required global regulatory and quality focus.

It is also useful to consider that very small changes in development programs may lead
STRATEGIES TO SELECT, ASSESS, FORMULATE, AND DELIVER THE RIGHT DRUG CANDIDATE IN THE EARLY PHASE

Major changes in outcomes. Other considerations include awareness of and avoiding various kinds of bias that include:

- **confirmation bias** (i.e., the tendency to do experiments that confirm rather than challenge),
- **endowment theory** (i.e., losing [in terms of development programs] is more painful than equivalent gains),
- **mental accounting** (in terms of CMC-related development, what is the bargain, what is not a good tradeoff), and
- **present bias** (i.e., giving greater weight to more near-term milestones when considering trade-offs between two future milestones).

Investment, timing, planning, and executing the plan are other elements that are important to consider in order to generate the best information in the shortest possible time. In terms of the investment plan, this includes knowing how well the plan is being executed with respect to the desired results and available funding. At the same time, the plan should incorporate an understanding of the risks inherent in failure and success as well as the flexibility to take advantage of unexpected opportunities.

CMC development is the cumulative effort of several teams. It is important to be mindful of what individual team members are thinking and communicating to ensure that everyone knows how their individual contributions affect the whole project. It is vital that everyone understands the plan and its risks so that it can be successful.

**Quality by Design at the Discovery and Early-Development Stages**

Along the early-stage development continuum, application of Quality by Design (QbD) concepts during early-stage drug discovery can facilitate the development of high-quality drug candidates that elicit a pharmacological response as well as address early-stage attrition (see Figure 3). For example, one of the key challenges is the design of drugs that conform to Lipinski’s Rule of 5 (RO5), which is just one of many drug design paradigms. The elements of RO5 include:

- an orally active drug should contain no more than 5 hydrogen bond donors;
- no more than 10 hydrogen bond acceptors;
- no more than 10 hydrogen bond acceptors;
• a molecular mass of less than 500 Daltons;
• and an octanol–water partition coefficient, log P, not greater than 5.

However, the reality is that early drug leads developed by combinatorial methods are often outside the limits of the space defined by RO5 (see Figure 4). The resulting impact, and a primary cause of increased lead attrition, of increasing log P and molecular weight, is decreasing solubility and, potentially, bioavailability (and biopharmaceutical activity). High lipophilicity has been linked to toxicity, poor solubility, and metabolic clearance (see Figure 5). As of 2006, 90% of the new chemical entities generated by high-throughput combinatorial methods have poor aqueous solubility (as classified by the Biopharmaceutics Classification System [BCS]), which affects bioavailability.

But, BCS is considered a regulatory tool that is useful in late-stage development and getting a biowaiver rather than early-stage development. Instead, for early-stage development, the Developability Classification System (DCS), proposed by James Butler of GlaxoSmithKline (Harlow, UK) and Jennifer Dressman of Goethe University (Frankfurt am Main, Germany), focuses on intestinal solubility, the compensatory nature of solubility and permeability in the small intestine, and an estimate of the particle size needed to overcome dissolution rate limited absorption (see Figure 6).

In addition to designing in solubility and other desirable biopharmaceutical characteristics along with the application of DCS, other tools are available to assess and predict metabolism and degradation allowing toxicity and undesirable reactive

- Outcome of using combinatorial and high throughput chemistry is marked increase in cLogP/MW and non drug–like properties
- Significant impact on solubility and potentially bioavailability (dependent on dose)

If an estimate of human clearance is available, time-plasma profiles can be predicted:

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Cmax (µg/ml)</th>
<th>AUC (µg/ml*h)</th>
<th>t½ (h)</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>0.15</td>
<td>1.6</td>
<td>3.0</td>
<td>13</td>
</tr>
<tr>
<td>Compound 2</td>
<td>1.90</td>
<td>10.2</td>
<td>1.8</td>
<td>31</td>
</tr>
<tr>
<td>Compound 3</td>
<td>0.005</td>
<td>0.03</td>
<td>2.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Compound 4</td>
<td>1.18</td>
<td>3.9</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Compound 5</td>
<td>0.71</td>
<td>4.8</td>
<td>3.8</td>
<td>36</td>
</tr>
</tbody>
</table>

Cmax = highest concentration (µg/ml)  
AUC = Area Under Curve (µg/ml*h)  
t½ = half-life of compound in plasma (h)  
F = oral bioavailability (%)  

Which molecule is the best?
metabolites to be \textit{designed out}. These include:

- an \textit{in silico}-based tool that describes/predicts the metabolic fate of a drug candidate;
- a tool that predicts chemical degradation;
- an \textit{in silico} system that can be used to qualitatively predict possible toxicity based on chemical structure; and
- a technology for the discovery of new chemical entities that target G-protein coupled receptors.

\textbf{Formulation Tools for Early-Stage Development}

Using the physicochemical properties of the optimized drug candidates and physiologically based pharmacokinetic (PBPK) models, the fraction absorbed, time-plasma concentration profiles, and oral bioavailability can be predicted (see Figure 7). Coupled with the DCS and other quantitative information, a best drug candidate can be selected for formulation development (see Figure 8).

Combining advanced \textit{in silico} PBPK modeling tools and parallel formulation screening approaches such as the OptiForm® Solutions Suite, the effect of particle size and different formulation technologies (e.g., lipid-based drug delivery system, hot-melt extrusion, spray drying, and micronization) and how they affect solubility, fraction absorbed, bioavailability, and \( C_{\text{max}} \) can be assessed and the formulation-related elements further optimized. This combination approach avoids formulation development work that is targeted at hitting a partially defined or wrongly defined biopharmaceutical target (i.e., increased absorption, extended half-life, etc.) without considering all phases of pharmacokinetics (absorption, distribution, metabolism, and elimination).

\textbf{Table: Picking the right molecule based on:}

<table>
<thead>
<tr>
<th>molecule</th>
<th>Efficacy</th>
<th>DCS class</th>
<th>( F_s ) 500 mg (%)</th>
<th>( F ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>5</td>
<td>IV</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>Compound 2</td>
<td>2</td>
<td>IIb</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>Compound 3</td>
<td>4</td>
<td>IIb</td>
<td>39</td>
<td>0,3</td>
</tr>
<tr>
<td>Compound 4</td>
<td>1</td>
<td>IIa</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Compound 5</td>
<td>3</td>
<td>I</td>
<td>100</td>
<td>36</td>
</tr>
</tbody>
</table>

\textbf{Conclusion}

Early-stage development is fraught with high rates of attrition due to one or a combination of the lack of lead compound solubility in water, poor DMPK, poor bioavailability, and high toxicity. The application of QbD concepts at the molecule design stage allows solubility and other desirable physicochemical properties to be \textit{designed in} and toxicity and other undesirable properties to be \textit{designed out}. Use of the DCS and \textit{in silico} PBPK modeling at the early stage of development allows for faster assessment of solubility and bioavailability, and coupled with formulation tools, faster assessment and selection of suitable formulations. In addition, implementing teamwork, team collaboration and interaction, and communications concepts across and within teams are just as important as knowledge-based factors. A team’s interactions, communications, and collaborations, and understanding of and engagement in the investment risks inherent in the development continuum enables the exploitation of \textit{good news moments} and development program success.

\textbf{Catalent is a leading global provider of advanced delivery technologies, development solutions, and clinical supply services for drugs, biologics, and consumer health products.}