Pharmaceutical companies are struggling to do more with less, and as resources diminish, patents expire, and competition increases, companies are striving to reach critical drug development milestones faster despite the chemical and physical challenges of the active pharmaceutical ingredient (API) candidate. This article outlines why opting to fill capsules with neat API to speed development of clinical supplies may not, in fact, be the most expeditious approach.

Lacing neat API in a capsule is a common approach to manufacturing Phase I supplies. In some cases, API-in-capsule shortens overall development by as much as 6 months because it reduces or eliminates time spent on formulation, analytical development, and stability testing. Developing placebos is also simple, and many pharmaceutical companies see it as a quick-fix option for meeting aggressive Phase I start dates.

But there are trade-offs. While the API-in-capsule approach may save time and get your candidate API into clinical studies sooner, it doesn’t eliminate the need to develop a formulation or optimize the manufacturing process. It is therefore critical to weigh the impact of API-in-capsule on your overall development plan—including its timeline and cost—versus using a formulated product in early studies. Table 1 lists the advantages and disadvantages of the API-in-capsule approach.

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<thead>
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<th>Table 1</th>
<th>Pros and cons of the neat API-in-capsule approach</th>
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<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
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<tr>
<td>Short manufacturing time</td>
<td>Higher overall drug development costs</td>
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<td>Minimal need to characterize API</td>
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<td>Suitable when API is scarce</td>
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Beyond API-in-capsule

Instead of relying solely on API-in-capsule, sponsors should evaluate another strategy—one that incorporates co-processed excipients—for developing oral dosage forms, particularly for first-in-human studies. From a scientific perspective, using excipients makes sense because conducting Phase I trials with a clinically relevant dosage form—whose manufacture and performance can be reproduced at a commercial scale—can add significant value to early clinical trial data. It can also reduce the risk of later-stage complications.

After all, when researchers are forced to change the dosage form during the clinical-development phase, risks increase significantly, and years may be added to development as the product’s clinical performance changes. Often, such changes occur between the toxicology stage and Phase I and Phase II trials, complicating researchers’ attempts to bridge early-stage data to later-stage clinical data.

For example, if first-in-human studies are conducted using neat API in a capsule, complications could arise in Phase II studies that are conducted using a formulated dosage form if the clinical data aren’t comparable. That could force researchers to perform another Phase II study or even another Phase I study. At the very least, it would require a crossover study.

Given the competitive nature of the pharmaceutical industry, having to repeat Phase I or Phase II studies could jeopardize the development of a product and/or the success of the sponsoring company itself. Too often those of us working in product development discover that a second Phase I or II formulation is required, usually because we didn’t completely understand how the dosage form performed or how formulation changes made ahead of clinical trials could affect that performance.

The appeal of QbD

To avoid or mitigate these risks, consider adopting a systematic approach to dosage form development using Quality by Design (QbD). It’s an approach that continues to gain acceptance in the pharmaceutical industry, especially for developing new dosage forms and filing abbreviated new drug applications (ANDAs). Indeed, as of January 2013, all ANDAs for products to be marketed in the USA must include QbD elements. For new drug applications (NDAs), both the FDA and the European Medicines Agency (EMA) are operating pilot QbD programs. While little data is available about the success of the FDAs pilot program, it’s likely that one or more regulatory agencies will implement some form of QbD requirement for NDAs once the programs conclude. (Through September 2011, four of the 32 total NDAs the FDA received for new chemical entities (NCEs) contained some QbD elements. Data for 2012 and 2013 aren’t yet available.) It is also likely that NCEs now entering the clinical phases of development will have to meet some form of QbD requirement when the sponsors file NDAs.

The guidances on QbD are available from the International Conference on Harmonization (ICH) in documents Q8, Q9, and Q10, which have been adopted by the EMA, the FDA, and Japanese authorities. The QbD elements that pertain to pharmaceutical development are the quality target product profile (QTPP), critical quality attributes (CQAs), risk assessment, design space, control strategy, and product lifecycle management. Definitions of each element and details about them are presented in clear detail in the ICH guidances.

The elements most relevant to the early stages of product development are QTPP, CQAs, and risk assessment. The design space, control strategy, and product lifecycle management are more applicable to later phases of product development (phases II and III and marketing applications).

Establishing a QTPP provides a very clear and comprehensive framework from which you can initiate product development. Establishing the QTPP and understanding the CQAs will, in turn, enable you to perform a risk assessment. The assessment should evaluate all factors involved in drug product manufacture and the potential for those factors to affect the QTPP and the product’s CQAs.

That means assessing the API, excipients, and all the steps in the manufacturing process. For an API-in-capsule formulation, this would include the API, the capsule, the capsule filling process, and the packaging process. For a formulated dosage form, many more factors would be involved, including excipients and the additional processing steps (i.e., granulation, blending, and tablet compression).

These additional factors produce a more complicated risk assessment and, as a result, a more time-consuming development program, which would seem to favor an API-in-capsule approach. After all, the simpler the dosage form, the lower the risk of developing problems that could prevent the start of clinical trials. But performing clinical trials using a dosage form that is not commercially viable also entails risk. In fact, it puts the product’s overall development at risk. Plus, since you need to conduct compatibility studies of the API and the capsule shell anyway, it makes sense to study excipient compatibilities as early as possible. That can be done with a well-designed excipient-compatibility matrix, which should take no more time on stability than the compatibility studies of the API and the capsule. Naturally, the additional analytical time devoted to the excipients would add cost.

Yet both cash and timelines are tight, and many of us cannot afford to place product and process development
on a QbD-inspired critical path toward product launch. In fact, moving toward a launch is often a high-risk, high-reward journey that conflicts with the principles of QbD. That’s why first-in-human studies are typically performed using API-in-capsule or API-in-bottle formulations: They offer a shortcut, a fast way to generate clinical data. But those forms also can prolong development since the API-in-capsule process cannot be scaled up to commercial production. And again, the clinical data based on API-in-capsule trials may not be relevant to the desired dosage form, especially if the final dosage form you’re seeking is a controlled-release product.

Given the vast risk, both financial and clinical, associated with early-phase development, we need approaches that reduce the risks associated with API-in-capsule strategies and that don’t prolong overall clinical development.

**QbD and co-processed excipients**

One solution is to apply QbD principles when developing product prototypes and to use co-processed (functional) excipients. Co-processed excipients can reduce the total length of time spent developing a dosage form that is clinically relevant. These excipients are available from many vendors and can be used in orally disintegrating tablets, immediate-release tablets and capsules, controlled-release tablets, and many other dosage forms.

Co-processed excipients are usually well characterized by the manufacturers and are designed with commercial manufacturing in mind. Thus critical excipient characteristics (particle size, flowability, compressibility, dissolution, disintegration, etc.) have been engineered into them. As a result, they eliminate the need to characterize many process parameters associated with dosage form development. In addition, many vendors offer case studies of drug products that demonstrate the application and performance of their products.

Based on the degree of engineering and characterization specific to the dosage form being developed—coupled with a simpler manufacturing process—co-processed excipients can eliminate some manufacturing steps and thus reduce the total time required to develop a dosage form for first-in-human studies. As a result, you have a much better chance of developing a dosage form that is clinically relevant in the early phases.

This was proven last year when we took a QbD approach in developing a solid oral dose for first-in-human trials. In that case, we developed both an API-in-capsule formulation and a tablet formulation. The two were developed, manufactured, tested, released, and shipped in the same amount of time.

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Adam Lambert, Ph.D., is director, preformulation and analytical chemistry at CoreRx, 14205 Myerlake Circle, Clearwater, FL 33760. Tel. 727 259 6950. Website: www.corexpharma.com.