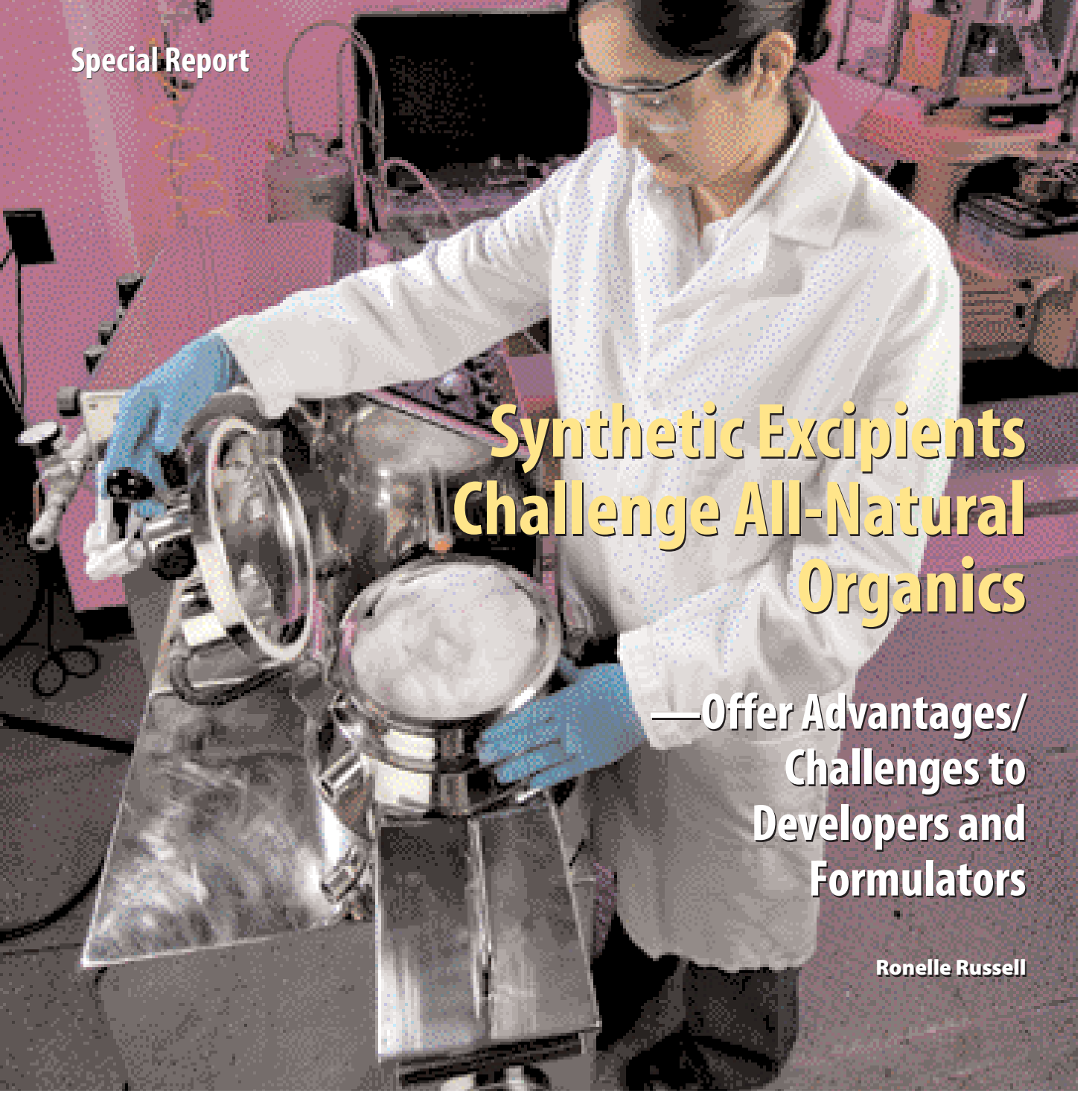


# Synthetic Excipients Challenge All-Natural Organics

## —Offer Advantages/ Challenges to Developers and Formulators

Ronelle Russell

**Synthetic excipients frequently offer advantages over all-natural compounds. However, manufacturers face various challenges with respect to their use, the biggest of which is often obtaining regulatory approval.**

Synthetic excipients have become commonplace in today's pharmaceutical dosage forms. Both synthetic and semisynthetic products have enjoyed a long history of use, frequently offering unique properties and advantages over all-naturally derived compounds, including a low sensitivity to various ingredients or moisture, resulting in more efficient and effective pharmaceutical products. But despite the many potential benefits of synthetics, manufacturers must still address a number of challenges before their current universe of implementation can be expanded.

The terms *synthetic* and *semisynthetic* are both broadly used to distinguish this family of excipients from those extracted from natural sources (plants/animals) such as starch, lactose, and microcrystalline cellulose (MCC). There are, however, also shades of gray and subtle nuances between the two types.

*Semisynthetic* typically refers to a substance that is naturally derived but that has been chemically modified. Most excipients in use today fall into this category. In contrast, *synthetic* is usually defined as a pure synthetic organic chemical that is derived from oil or rock.

## An excipient's path to the *National Formulary*

After a new excipient has been used in an FDA-approved drug, the excipient manufacturer can submit a monograph of the excipient to the United States Pharmacopeia (USP). USP's web site, www.usp.org, posts the requirements for new submissions, called "Requests for Revision," and details what should be included in the submission package.

Once USP receives the company's submission, it first makes an initial evaluation of the completeness of the data. If it determines that all the required data are included, it will send the submission on to an expert committee for review. The committees are generally composed of representatives from the pharmaceutical manufacturing industry, government (including FDA), and academia.

The expert committee will then make a more-thorough evaluation of the submission package. If accepted, it will be incorporated in the *Pharmacopeial Forum* (*PF*), which is published every other month, for public review and comment. Anyone with an interest in that excipient, called a stakeholder, can send comments, but those comments must be substantiated with appropriate data or reasonable information.

After the comments are received, the complete package is sent back to the expert committee. If there are no comments, the monograph proposal is voted on by the expert committee to become an official monograph in the *USP–NF* after a minimum of 60 days (typically 90 days) have passed since its publication in the *PF*.

When there are comments, the committee will decide whether to revise the monograph accordingly or to reject them. If the monograph is revised, then it must be published in the *PF* a second time, then can be voted to become an official monograph 60 days after publication. If a monograph requires only one publication in the *PF*, it can become official in approximately 6–8 months. When a second publication cycle is required, the entire process can take 15 months or longer.



Excipient manufacturers easily disagree with these definitions when describing their products because so much chemistry is involved in the manufacturing process. As a result, the term *synthetic* is frequently used to encompass both types.

### Applications and advantages

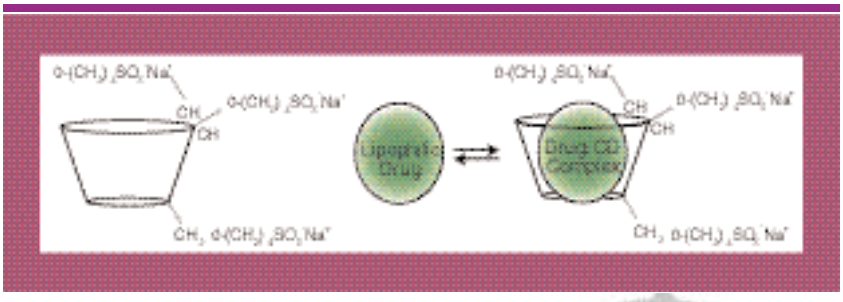
Synthetic excipients are used in the manufacture of tablets to bind the tablet together, reduce die-wall friction between the tablet and the tableting press, control pH balance, and to disintegrate the tablet in the stomach once it has been ingested. They're used for just about every function of an inactive ingredient except as bulking agents, which are usually natural products. In parenterals, synthetics are used as solubilization agents to make actives more soluble, and therefore, more deliverable.

Synthetics also offer other benefits over natural excipients. Because they're not extracted from animal materials, they're free of transmissible diseases—a characteristic that may be of increased importance among manufacturers and regulators in light of the recent case of a BSE-infected cow found in the United States last year. The absence of plant or animal material in synthetics also eliminates concerns posed by genetically modified organisms (GMOs), which can also interfere with the safety and acceptability of a drug formulation.

Another benefit of synthetics compared with natural excipients is that they can be produced to a certain specification because there is more control over the manufacturing process. Most natural-based polymers aren't chemically identical because of the variability that exists in nature. For example, depending on changes in weather from one year to the next, the structure and properties of natural materials can also vary slightly—an effect avoided with synthetics, which are synthesized in chemical reactors.

Joseph Zeleznik, senior scientist at excipients manufacturer JRS Pharma (Patterson, NY), points to magnesium stearate as a good example of a natural material versus a synthetic. "Manufacturing controls are just not that stringent because they can't be. Because magnesium stearate is a naturally derived product, it possesses a great deal of inherent variability—not only from batch to batch but from manufacturer to manufacturer as well," says Zeleznik.

Such variability in natural excipients can be problematic for drug manufacturers because once their formulation has been approved by FDA, it becomes difficult to change the formulation components or component levels that were used in the clinical trials. If any variability exists, either in the raw materials or manufacturing process, a company will have to spend more time and money proving that there are no adverse effects as a result of the change.




Lipophilic drugs form an equilibrium complex with the lipophilic cavity of cyclodextrin molecules, minimizing their interaction with water. The hydrophilic nature of the exterior of the cyclodextrin provides water solubility for the drug-cyclodextrin complex.

Eric Smith, vice-president of marketing at JRS, agrees with Zeleznik. "Even slight changes, such as in particle size, can affect the drug release profile," Smith says. "Our industry is really exacting with specifications."

JRS Pharma manufactures the excipient "Pruv" (sodium stearyl fumarate), which is used as a boundary lubricant (i.e., it coats the powder particles in formulations) and also helps reduce interparticulate friction to enhance formulation flow onto the tablet press. "Lubrication is a very sensitive function within the tableting process," Smith states. "The key is to produce a synthetic material that always delivers the same lubricity level to the formulation." Because of the sensitivity of the lubrication function, companies impose strict specifications on manufacturing processes to ensure the predictability of products.

## Bringing new synthetic excipients to market

One of the main challenges facing synthetic excipient manufacturers, as they drive toward higher market share, is the difficulty involved in bringing a new synthetic excipient to market.

According to Lou Blecher, former chairman of the International Pharmaceutical Excipients Council (IPEC) and now a consultant to excipient manufacturers, this particular challenge is a "virtual impossibility" for synthetics manufacturers. As Blecher explains, because FDA has no regulatory body to review excipients separately from formulations, they're only approved as part of a new drug application (NDA) or investigational new drug (IND). In addition, the United States Pharmacopeia (USP) will not add any excipients to its *National Formulary* unless the excipient has been used in at least one FDA-approved product.

Although these regulatory issues may sound like obstacles in and of themselves, the real difficulty lies in convincing drug manufacturers to use a new excipient in a formulation. Typically, manufacturers won't risk product approval with a novel synthetic unless that particular excipient provides a unique function essential to the formulation. "Why would you ask for the extra trouble of having to explain something to the FDA reviewer that he or she has never seen before?" Blecher queries. "It's much easier to stick with materials that are already accepted than to monkey around with something new."

Lokesh Bhattacharyya, PhD, director of the noncomplex actives and excipients division in the information and standards development program at USP, agrees with Blecher and adds that because the functions of new excipients are less understood, there's more concern about their affect on the bioavailability of a drug product. "Anything new will get more scrutiny," he says. "A new excipient will require a greater level of categorization."

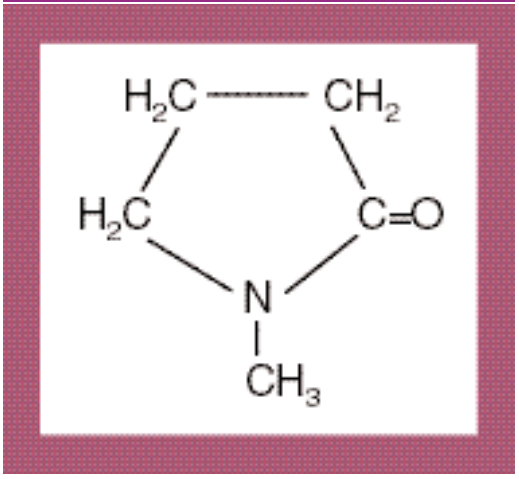
**Finding profitable applications.** For a drug manufacturer to consider using a novel synthetic excipient (a brand new chemical that has not been used in drugs before), the excipient manufacturer will have to develop the same amount of safety data required for a new drug, which is both costly and time consuming. This fact alone prevents many synthetics providers from developing new products unless there's a specific application for the novel excipient that can outweigh the costs of safety testing and prove profitable for the company. "If it's not the only thing permitting an antitumor agent from being marketed, are you going to spend the money looking?" asks Blecher.

CyDex, Inc. (Lenexa, KS) decided it would spend the money when it produced its novel excipient, "Captisol" (modified beta-cyclodextrin). Captisol, which is considered a semisynthetic excipient because it's a chemical modification of parent cyclodextrins that occur in nature, works as a solubilization agent, allowing anticancer agents to be delivered parenterally to the body.

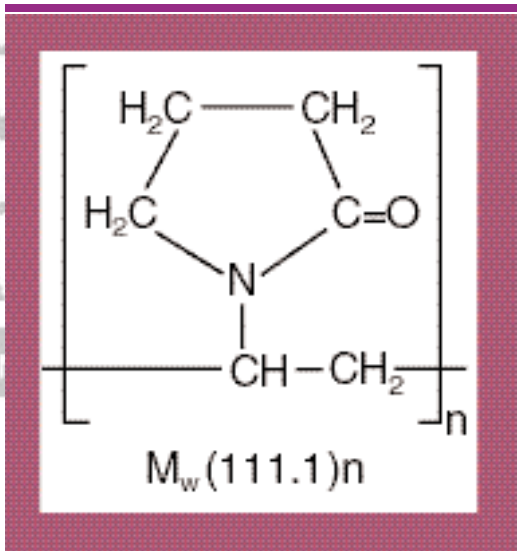
The development of Captisol was motivated by an overall interest in the use of cyclodextrins for parenteral formulations. Beta-cyclodextrin can't be used in parenteral formulations because, upon systemic administration, it causes extensive hemolysis and dramatic nephrotoxicity. Researchers such as those at the University of Kansas explored modifications of the parent cyclodextrins in search of derivatives that would have good systemic safety profiles while retaining or improving the functional complexation characteristics of the parent cyclodextrins.

Because the safe delivery of anticancer agents is such a strong need in the industry, CyDex decided it was a viable application for this type of excipient. Doug Hecker, director of operations at CyDex, states that it's best for a manufacturer if an application for a new excipient comes from the customers themselves. "It's easier to solve a known problem than to try to find a problem and then

Plasdone (povidone) with tablet punches.




The molecular structure of Pharmasolve (N-methyl-2-pyrrolidone).




The molecular structure of Plasdone (povidone).

solve it," he says. Hecker also explains that the unique properties of Captisol make it the kind of excipient that actually helps bring certain drugs to market that otherwise couldn't move forward into clinical studies. "We provide an alternative that helps with a formulation, and in some instances, makes the formulation," he states. "It's an enabling technology." Captisol is currently used in four approved parenteral products—two in the United States and in two in Europe.

**Receiving GRAS status.** One way that many new excipients make it into oral dosage formulations is by using materials that FDA classifies as generally recognized as safe (GRAS). However, GRAS status primarily applies to materials that are also used as food additives, and requires companies to submit a food additive petition to FDA.

In some instances this is a viable option, because many excipients in use today are materials that were, in fact, previously used in the food industry. However, Captisol represents an example where this wasn't the case. Captisol isn't used in food, and although it does have some applicability in oral formulations, it's main use is for solubilizing drugs for injectable products.

**Assembling a Drug Master File.** Although CyDex may apply for GRAS status for Captisol in the future, it has, in the meantime, still been able to promote its products to drug manufacturers because its safety and chemistry, manufacturing, and controls (CMC) data are available in a Type 5 Drug Master File (DMF). Whenever a drug containing Captisol is in clinical trials, CyDex provides the company with a letter of authorization to the DMF that allows FDA to review the safety information about the novel-enabling excipient. Although drug formulators aren't required to supply FDA with a DMF when using a new excipient in their formulations, a DMF can be helpful to FDA reviewers during the drug approval process, and formulators are always looking for additional information that will help them get their drugs approved.

"GRAS status applies to use in foods and often translates into some broad acceptability for use in pharmaceuticals," says J.D. Pipkin, PhD, director of product development at CyDex. "But if your product doesn't have GRAS status, then you have to supply your safety data and be convincing with it for each and every application," he says.

**Coprocessing.** Another way that new synthetic excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical is by coprocessing previously accepted materials such as two already-established excipients. Many synthetic and semisynthetic manufacturers, such as International Specialty Products (ISP, Wayne, NJ), are using this approach to add new excipients to their product base. "If there's a drug application in which none of the standard excipients will work, then you have to look for something new," says Tim Bee, PhD, director of marketing pharmaceuticals at ISP. "But

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in most cases you can use the standard ingredients in different ways to do what you need to do."

Bee doesn't see a broad-based need for totally new synthetic excipients for basic tablets or parenterals, which means that companies like ISP must look for other ways to grow. "No customers are coming out and saying that they need a significantly better tablet binder," he says. "They would certainly love to have something that worked better, but something that would be chemically totally different would require too much new safety data and would be difficult to justify economically without a strong market pull." Though Bee agrees that some niche applications in drug delivery and targeted-release formulations do need new excipients, he feels that, "for most areas, totally new materials are not required."

ISP has addressed this lack of new applications by providing new ways of processing previously-accepted materials that can help lower drug manufacturers' costs or extend the patent life of their drug. "An excipient manufacturer has to focus on providing tablet manufacturers new ways of doing things because pharmaceutical companies are also looking to offer new things to consumers," Bee says.

USP's Bhattacharyya agrees, but adds that as more new products such as aerosols, modified-release tablets, and a variety of new drug-delivery systems come to market, there will be opportunities for excipient manufacturers to develop all-new excipients as well. "Everyday we hear about new, more-effective, easily deliverable products. These new products will need new excipients that are suitable for new and novel formulations," says Bhattacharyya.



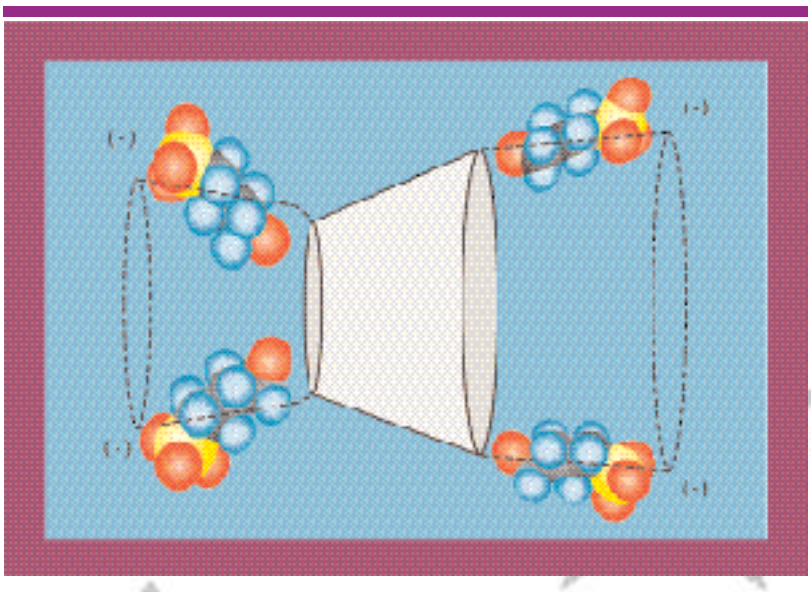
ISP currently manufactures "Plasdone" products (povidone), which are used as tablet binders and as solubilization agents in parenterals; "Polyplasdone" (crospovidone), a disintegrant; "PharmaSolve" (N-methyl-2-pyrrolidone), a solubilization agent for parenterals; and "Cavamax" (cyclodextrins), a solubilization agent sold by ISP through an alliance with Wacker-Chemie GmbH (Munich, Germany).

## Getting an excipient monograph in USP's *National Formulary*

Once a new excipient has become part of an FDA-approved formulation, the excipient manufacturer can submit a proposed monograph to USP to be included in the *National Formulary* (*NF*), one of two compendia included in the *USP–NF*. The pharmacopeia will then develop a quality standard (also called a monograph) for the new excipient through a scientific-review process that begins with evaluation by an expert committee and includes an opportunity for public comment. The entire process can take anywhere from 6 to 15 months (see Sidebar, "An excipient's path to the *National Formulary*").

After the review process is complete, the monograph is then added to the *USP–NF*, which provides validated analytical procedures and associated acceptance criteria for drug substances, products, and excipients.

There are a variety of reasons why excipient manufacturers would want their novel excipients to be included in the *USP–NF*. First, the formulary publishes the highest quality standard for the product publicly available, giving drug manufacturers more



The sulfobutylether substituents on Captisol enhance complexation by providing an extended hydrophobic cavity and an extremely hydrophilic exterior surface.

confidence in the quality of the product, which can translate into higher sales for an excipient company.

Also, if there's another manufacturer for the same excipient subsequent to the development of the monograph, then it will have to comply with the quality standard already published in *NF*. Consequently, the company that submits a new monograph has a greater role in developing the tests, procedures, and acceptance criteria that should be performed when evaluating quality of the substance.

And when drug manufacturers buy NF-grade materials for their products, they can be assured that the appropriate tests and procedures have been used, and that the quality standard is appropriate for their product. FDA inspectors also have a high degree of confidence in NF-grade materials and generally will not question the tests and acceptance criteria used.

**Must-have GMPs.** The path to inclusion of an excipient monograph in the *National Formulary* is not without obstacles, however. For example, one potential difficulty is that USP requires the excipient to be manufactured using good manufacturing practices (GMPs) for pharmaceuticals. Since, in many cases, the excipient material is used primarily in other applications such as food, cement, or paint, which don't require the same level of manufacturing standards, manufacturers will often have to incur significant additional cost to meet the USP's GMP requirements.

"We're working with excipient manufacturers to come to a mutually acceptable approach in

these areas," says USP's Bhattacharyya. "The quality versus cost issue is a difficult one, and we always have to find a balance."

**Incomplete data and proprietary information.** Another potential problem is within the monograph submission itself. If a company doesn't provide complete data in the submission, valuable time can be lost.

Misunderstanding or inexperience with the process requirements may not always be the reason for an incomplete submission. Sometimes companies deliberately withhold data because of concerns about releasing proprietary information.

Although he understands these concerns, Bhattacharyya notes that this can be a problem, because the expert committee has a responsibility to decide what data are necessary to develop an appropriate quality standard. "Though we respect the manufacturers' need for proprietary information, we also don't compromise on the highest level of quality standards," explains Bhattacharyya. USP has a document disclosure policy that serves to protect confidential information and intellectual property rights. "In almost all cases, we finally come to an agreement, but it can take a considerable amount of time," he says.

## Future of synthetic excipients

JRS's Smith believes that coprocessing could hold the key to a successful future for synthetic excipients by ushering in a new class of multifunctional compounds. "It's a formulation industry, therefore people are always coming up with different excipient combinations," says Smith. "Formulators have many tools they can use to obtain their defined dissolution rate. A new excipient is just another tool."

Blecher agrees with Smith's forecast and adds that synthetics and semisynthetics will be used by the industry for many years to come, as long as excipient manufacturers keep finding new ways to make things simpler for the drug formulator. "Anything that will do the job better, more efficiently, and more dependably will always be of interest," states Blecher. PT