

Pharmaceutical Technology®

SPECIAL REPORT

Debating Excipient Functionality

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While talks continue about whether excipient functionality-related characteristics belong in a pharmacopoeia, suppliers and users seek to reduce variability without imposing overly restrictive specifications, introducing irrelevant testing, and jeopardizing harmonization.

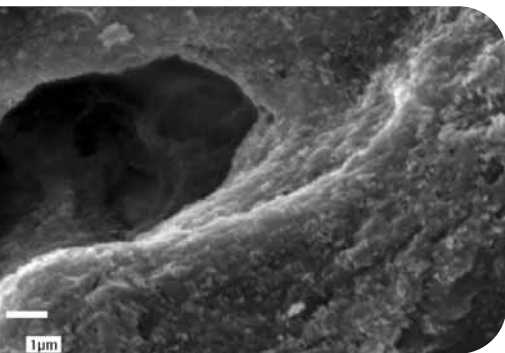
Raw materials are one of the main sources of batch-to-batch variation. Although analytical tests evaluate whether a material is within physical and chemical limits, manufacturers are well aware that conformance to pharmacopoeial specifications does not provide sufficient confidence that an excipient will perform according to its intended purpose. Certificates of analysis, therefore, provide little information about what the industry has termed *excipient functionality*. It is not uncommon for analysts to conduct exhaustive up-front tests on variations of an excipient from different sources to confirm equivalence-

and then to find, when these materials are used in production, that one variation will work and the other will not.

Currently, material documentation and regulatory guidances offer very little information about functionality. Pharmacopoeial compliance demonstrates analytical purity. The limited physical testing that is performed reflects functionality only indirectly. For example, a material's density and particle size will provide some insight into its flow, but it will not provide information about the properties it brings to a dosage form during manufacture, under specific applications and processes, and

in the presence of other ingredients in a formulation.

Functionality has become a hot-button issue recently because the European Pharmacopoeia (EP) plans by April or May 2007 to list specific functionality-related characteristics (FRCs) in some of its excipient monographs. Earlier this year, EP released a draft of one of the monographs that includes the FRCs for an excipient deemed to be typically important by the EP's Expert Committee. They also have proposed an associated General Chapter that describes the approach they plan to use to address FRCs when they are listed in monographs. The



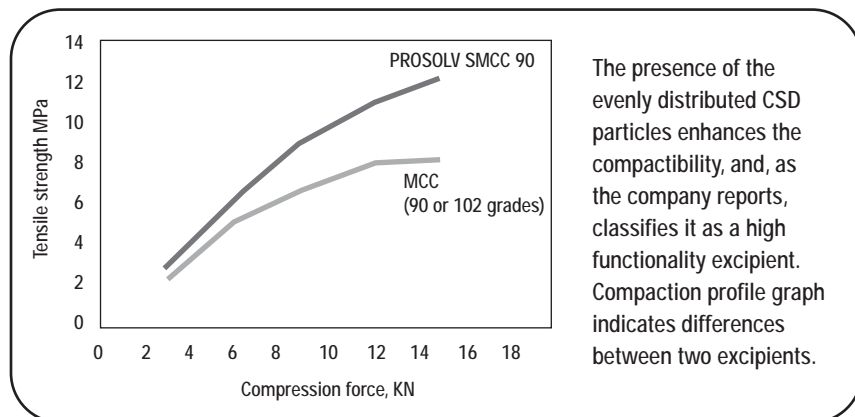
SEM shows the uniform distribution of colloidal silicon dioxide particles on the surface of the MCC as a result of co-processing (PROSOLV, JRS Pharma).

EP describes these tests as nonmandatory but recommends that the tests should be considered because of their importance to the excipient's performance in many applications

USP also has looked into including a General Chapter on Excipient Performance Testing—specifically disintegration, compactibility, and lubricity—suggesting it could be part of the labeling section and nonmandatory (1). Some excipient makers have voiced strong opinions about who is to gain from the increasing focus on functionality as it relates to pharmacopeial requirements and recommendations. One excipient manufacturer states, “There is cynicism in the industry. When you consider the number of advisory academics that also have analytical consultancy interests, it makes you wonder.”

In the eye of the beholder

Part of the debate centers around the true meaning of *functionality*. Of course, all excipients serve a function or a purpose; otherwise, they would not be included in the formulation. Today, however, excipient functionality refers to an excipient's contribution to a dosage form's stability, identity, delivery, and processability. The actual functionality depends not only on intrinsic excipient properties, but also on details of the application, the formulation, and process. “The complication is that functionality goes beyond the excipient. Guaranteed functionality in isolation does not exist. You add an excipient for an intended purpose and that is its



The presence of the evenly distributed CSD particles enhances the compactibility, and, as the company reports, classifies it as a high functionality excipient. Compaction profile graph indicates differences between two excipients.

functionality or its utility in that formulation,” says Brian Carlin, global manager, Pharmaceutical R&D, FMC BioPolymer (Princeton, NJ).

“Everybody has the same meaning for functionality, but I don't think they understand the implications of what they're trying to describe,” says Chris Moreton, vice-president, Pharmaceutical Science, Idenix (Cambridge, MA). “Functionality, like beauty, lies in the eye of the beholder.”

Defining the functionality of an excipient may not be as easy as it seems. Many excipients are by nature multifunctional and produced in various grades. Microcrystalline cellulose (MCC) is compactable; it also wicks water and can aid disintegration without aiding compaction. “Does this mean it is important to determine its swelling capacity or other hydration characteristic?” asks Alen Guy, vice-president, R&D, JRS Pharma (Paterson, NY). “It's almost impossible for suppliers to measure functionality due to the numerous different ways that excipients may be used by their customers,” says Dave Schoneker, director, Global Regulatory Affairs, Colorcon (West Point, PA) and Chair-Elect of the International Pharmaceutical Excipients Council of the Americas (IPEC Americas).

Adding to the complexity, excipient users may not tell suppliers how they are using the material. In some cases, the material is used in applications the supplier never intended. Furthermore, some excipients are also actives. Dibasic calcium phosphate, mannitol, dextrose, for example, are regarded as actives in certain applications.

Most excipients originated in the food industry. Food excipients (unlike those for drugs) have more commonly understood functional specifications. The food industry purchases on functional and physicochemical specifications, whereas the pharmaceutical industry mainly relies on physicochemical specifications. “Functionality is much less understood in the pharmaceutical industry than in other industries such as the food industry. Pharmaceutical specifications emphasize analytical compliance with pharmacopeial requirements, which generally have little or no relevance to functionalities,” says Carlin. For example in purchasing carageenan, which is a material used in both food and pharma, pharmaceutical customers only want to know whether the grade meets the pharmacopeial requirements. In contrast, a food customer may specify that the excipient has to have a certain gel strength under certain conditions. And they will build that into their purchase specification. “I rarely see pharmaceutical customers provide functional specifications. Food ingredients might have variable composition to ensure consistent functionality, but consistency of composition generally takes precedence for pharmaceutical excipients,” says Carlin.

Hype or high function?

Terms such as “high-functionality excipient” (HFE), which has been used in the market, and “critical excipient,” which has been used in the literature, may be even more ambiguous.

High functionality. There is no accepted consensus on distinguishing “high-

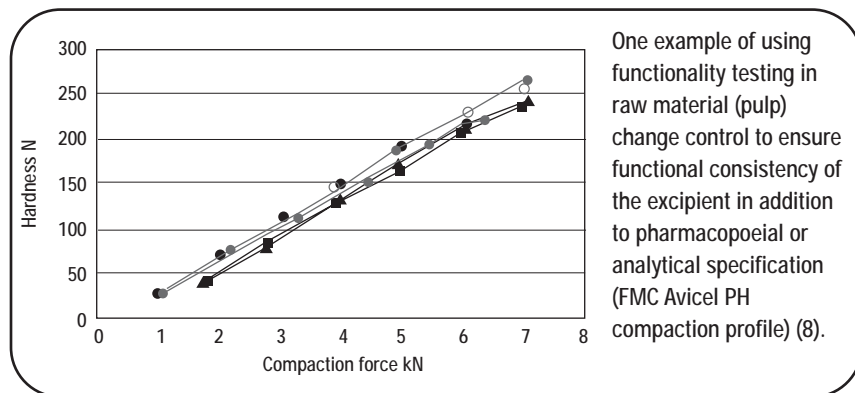
functionality” excipients from ordinary “functional” excipients. Some industry experts are convinced the term serves no purpose in describing excipient quality. “The term *high-functionality excipient* is a marketing construct and is somewhat meaningless in that rational formulators are not likely to use low-functionality excipients,” says Carlin. Moreton agrees, “You could argue that any material is highly functional in its application because without it the formulation won’t work.”

Some authors on the subject have stated that high-functionality excipients meet four criteria:

- HFEs are multifunctional. They will combine two or more functions usually provided by single ingredients, such as glidants, lubricants, antiadherents, binders, or disintegrants.
- HFEs have high inherent functional performance allowing for increased batch sizes and higher drug-loading, even at low usage levels.
- HFEs require no complex processing, making them ideal for direct compression processes.
- HFEs impart their high inherent performance characteristics to the overall formulation (2).

This last criterion reportedly distinguishes HFEs from other multifunctional excipients or conventional specialty excipients. “HFEs provide several functions to a drug formulation using fewer ingredients, simplifying final dosage forms and the manufacturing process,” says Joseph Zeleznik, associate director, R&D, JRS Pharma (2). “High functionality, in many instances, can merely be a special grade of preexisting excipient that generates improved functional performance for one functional characteristic, without improving overall material or formulation functionality.”

A high-functionality excipient meets one of three criteria, according to Anisul Quadir, technical development manager, Pharma Solutions, BASF (Roxbury, NJ): a high-functionality excipient is multipurpose (for example, it can be used as a binder, and it can be used as a stabilizer, or to improve dissolution); or the material can be used in a lower amount



One example of using functionality testing in raw material (pulp) change control to ensure functional consistency of the excipient in addition to pharmacopoeial or analytical specification (FMC Avicel PH compaction profile) (8).

and still outperform other conventional materials; or it can be used in multiple technologies such as wet granulation, dry granulation, extrusion-spheronization, or melt granulation.

Suitability for multiple processes may not be enough to establish a material as “highly functional,” however. “Saying an excipient can work in wet granulation, in direct compression, and in roller compaction is not the same as saying it is multifunctional in a formulation,” says Moreton. For example, “MCC and MCC-derived excipients are highly used because they have a lot of advantages and some good properties, but sometimes they don’t work.”

Critical excipients. Arvind Bansal, associate professor, Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (Punjab, India) explains that critical excipients are inert materials that can affect the characteristics, quality, stability, or performance of the drug product (3). An example of these are solubilizers and dissolution modifiers such as surfactants for BCS class II and IV drugs, wetting agents for hydrophobic drugs, preservatives in parenterals, pH modifiers, buffers and stabilizers in pH-sensitive drugs, antioxidants for drugs that are prone to degradation in the presence of air (4).

Even in small quantities, these materials can significantly affect the dissolution, bioavailability, and stability of dosage forms. “It is imperative to identify these excipients in the formulation and thoroughly characterize and quantify them. Regulatory authorities also ask for data that demonstrate whether the method is

sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients during manufacturing or during storage,” says Bansal, referring to US Food and Drug Administration guidelines on stability testing and Health Canada’s draft Quality Chemistry and Manufacturing Guidance (5, 6).

Not everyone agrees. “You could argue that for controlled release, a rate-controlling excipient or combination of excipients would be critical for the correct functioning of that product, but so are the other excipients,” says Moreton. In addition, “It’s hard to label a material that you changed as not critical, even if it’s just a filler. Switching from sucrose to sorbitol, for example, could actually reduce your bioavailability. And then other unanticipated criticalities can arise in your manufacturing. Even if you can get alternative excipient sources that meet your specification, you might have higher production difficulties that reduce your efficiency,” says Carlin.

Pharmacopoeial disharmony

Industry’s view. The disparities in definitions are only part of the reason many excipient suppliers and other organizations oppose the European Pharmacopoeia’s current efforts to include FRCs in its monographs. Although the excipients industry may not agree on the definition of functionality, many manufacturers do appear to be on the same page about putting FRCs in a monograph, even if testing for these characteristics is optional. “What happens is that in practice it gets into the hands of people, particularly analytical groups or purchasing managers,



International harmonization may slow down considerably.

with even less understanding of the concept. They will just look at the entire specification and want everything, whether or not they need it," says Carlin. "Regardless of what the pharmacopeia says, the monographs are regarded by a lot of people as 'it.' If it's in there, you have to test it," says Moreton.

Including functionality in a monograph "is not the way to go" says Moreton. "I've read the European draft general chapter and draft monograph proposal and, quite frankly, I don't know where they are coming from. Even in the current monographs there are issues. It doesn't make sense to me at all. Some of what they are asking for has little or no relevance to what we are trying to do." Evaluating the particle size of lactose is one example. "There are applications of lactose that do not depend on particle size, such as its use in film coating, but because particle size is part of the lactose monograph, people have to test for it, even if it is unnecessary. MCC is another example. One of the labeling items is the degree of polymerization, and the EP seems convinced that degree of polymerization is crucial to the function of that material. It's not. It's a consequence of other changes that do not necessarily affect functionality."

Specialty companies marketing pharmaceutical excipients are also voicing concerns. "The definition of functionality for someone who is using a polymer in a film coating application won't be the same as for someone who is using that polymer in a matrix tablet or as a binder," says Nasser Nyamweya, technical services manager, Degussa Pharma Polymers (Piscataway, NJ). Current monographs cover fairly straightforward standards for identity and purity, he says, but, "Because functionality may mean different things to different people, putting it in a monograph would be quite challenging."

IPEC's views. IPEC Americas chairman-elect Schoneker states clearly, "We really are strongly discouraging the pharmacopeias from including any listing of

functionality or physical testing related to functional properties in the monograph itself other than those which are necessary for the identification of the basic excipient type (such as viscosity or degree of substitution for polymers)." IPEC would prefer to include these properties in the mandatory section of a monograph. "To specify certain functionality tests for a particular excipient in a monograph, in a general way, appears to us to be very much the wrong way to go, regardless of whether they may be defined as nonmandatory by a pharmacopeia." Schoneker believes this approach will lead to tests being run by users and makers of excipients that are not necessary for the intended uses in many circumstances, adding cost to the product. In addition, "It may convince some user companies that they may not have to perform the appropriate process development evaluations that they need to do to identify the properties that really matter," he says.

IPEC Americas is supportive of having the pharmacopeias write a General Chapter that would help provide guidance on a systematic process for evaluating the appropriate properties of an excipient and the associated test methodologies that would be useful in a particular drug application as opposed to listing the properties for an excipient in a monograph. USP has initiated efforts to develop a chapter that appears to be aligned with this strategy.

The IPEC America position—that functionality is neither a pharmacopoeial nor a public-standard issue—has at times been misinterpreted as an objection by manufacturers to having functionality requirements and functionality testing at all. "That is completely the wrong thing to think," says Schoneker. "We fully understand the need for functionality testing and the importance it has to drug product quality. In fact, we support completely that it is necessary for users in a PAT and quality-by-design environment to understand the variation of key functionality-related properties and put to-

gether the best formulation and process that they can based on the consistency that can be achieved from their supplier's capabilities. The primary difference between IPEC America's view on this and that of some people within the pharmacopeias is that we believe that the identification of appropriate FRCs for an excipient is truly something that is the user's responsibility to determine for their specific drug and their process and that it is not something that can be generally applied to any given excipient, except in the case where the user has demonstrated and understood that these tests and these properties are meaningful."

Harmonization challenges. Including FRCs in the European Pharmacopeia and not in the USP will make harmonization difficult. "It's going to provoke a bit of disharmony in the harmonization process," says Carlin. Zeleznik agrees, "If anything suffers in all of this, it will be harmonization, which has been less than adequately completed because we can't agree on what we currently have. Now we're going to add functional performance and other criteria? Harmonization will come to a complete halt."

This situation will be worse for companies that market specifically to pharmaceutical companies. Customers on one side of the Atlantic will have one set of requirements, and customers on the other side will have another. "In the interest of harmonization, we have to go where the most [stringent] legislation is. Even if the US pharmaceutical industry doesn't include functionality specifications, from a regulatory standpoint, because the EP does include it, we've got to do everything according to EP to keep it harmonized," says Guy.

Self-inflicted wounds

An evolving market. International harmonization is becoming more important as the pharmaceutical excipients industry grows and evolves. Global pharmaceutical excipients revenues have been estimated at \$1.13 billion in 2004, with an expected growth at a compound an-

nual growth rate of 5.3% between 2004 and 2008, reaching \$1.39 billion in 2008, according to a Frost & Sullivan forecast (7). Although Europe and North America account for about 75% of the global excipients market, manufacturers from India and China are poised to enter the market within the next four years. Because both countries already have a strong presence in API and intermediates manufacturing, they are set to build on brand image and increase their presence in the market.

According to the report, bulk excipients such as MCC and lactose face continuing commoditization as manufacturers look to decrease costs. According to the Frost & Sullivan, "The need of the hour, therefore, is for companies to focus on understanding the customer's requirements comprehensively and managing myriad aspects such as technical and budgetary issues, regulatory issues and quality assurance. Excipient manufacturers that understand and follow such approaches are more likely to gain customers' trust and consequently, earn continuous business from them."

Tighter specs won't help. Focusing on customer requirements may not be an easy task, however. Excipient users are getting increasingly sophisticated in what they measure. They are starting to measure properties that nobody has ever looked at before. In some cases, they are establishing specifications for these characteristics without really talking to their suppliers to find out whether it is feasible to make the product to those specifications. As Schoneker points out, "Unless the excipient manufacturer does a very significant amount of business in the pharmaceutical sector, one of two things is likely going to happen: either the supplier is going to have to increase their price for the pharmaceutical grades because they are going to have to do a lot of extra testing and control or they are simply going to say, 'Go buy it elsewhere we're not messing around with our process.'" This latter situation is a real possibility for many excipient companies because whether they sell in the pharmaceutical industry is almost irrelevant to the bottom line; the volumes sold for pharma-

ceutical use makes up such a small portion of their annual output.

Even excipient companies focused on the pharmaceutical industry may not benefit from tighter specifications. "Tighter specifications may be good for one customer, but could adversely affect or not help another at all. For example, you could tighten the specifications on particle size for a direct-compression excipient, which could lead to better performance for customer A, but what effect would this change have on the drug product of customer B? You really have

The debate over functionality is not about to be settled anytime soon.

to evaluate the potential effects of making some of these changes, especially if you have a well established and widely used excipient," says Nyamweya.

Drug-company procurement habits pose another big problem. In many cases, excipients are bought by purchasing departments that, worried about questions from regulators, look only at pharmacopeial specification compliance. "Compliance to pharmacopeial specification only is somewhat of a lowest common denominator approach. Considering the some \$90 billion in operating costs of Big Pharma per year, which is more important, to save a few cents per kilo in raw material costs, or to enable a significant reduction in the very high operational costs that the industry is currently saddled with? I could see in the near future that rather than buying an 'off-the shelf' general grade you'll actually buy a bespoke grade specific to your optimized process," says Carlin.

Connecting functionality with material properties will require extra effort from purchasing managers, regulatory managers, and formulators. "If you look at ICH Q8 and the quality-by-design movement and PAT, it's all about doing the appropriate work to establish connections, not necessarily just forming tight

specifications. Tight specifications are the old way of doing it: where you really don't have information, you just keep tying everything down, hoping it is going to solve your problem," says Schoneker.

In some cases, a "guaranteed functionality" may not be desirable. According to Guy, "It could be true that by meeting consensus functionality, the minority of users that need a slightly different property from the base material will 'lose' the product." One example is hydrogenated vegetable oil. Hydrogenated vegetable oil is a liquid film lubricant whose crystal state is not essential to its functionality. "We have a customer that relies upon a less-than-perfect control over the polymorphism of that product. If we controlled this sufficiently so that it went over to one crystallized state or another, it would actually lose the functionality he was looking for his application. He is relying on not having tight control over the crystallized state of that material. He benefits from a lack of guaranteed functionality."

Pharmaceutical companies registering exact formulations and fixed processes may be disadvantaged if they expect to see zero variability in their raw material. "It doesn't work that way. If an unanticipated variability arises beyond the specification, it may not be technically or economically feasible for an excipient supplier to rescue the situation and avoid the customer having to seek a regulatory variation. Pre-PAT, this is often exacerbated because of overly narrow finished product specifications due to a very limited number of validation batches, not representative of variability over a longer range of production—a self-inflicted wound that could have been avoided by better raw material characterization and discussion with the supplier before registration."

Unlocking the benefits

The debate over functionality is not about to be settled anytime soon. "The PAT initiative will drive it more toward understanding functionality for excipients," says Carlin. "The characterization of functionality is very simply process understanding in accordance with the

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philosophy of the FDA PAT and 21st century GMP initiatives. Anybody who wants to unlock the benefits of the PAT initiative, has two choices." They can eliminate all excipients and do away with raw material variability. ("There are a few specialized technologies that will drive you that way, although it is not practicable," Carlin notes.) Or they can seek the regulatory relief offered by the PAT initiative and quality-by-design approach by demonstrating scientifically that they know what they are doing, including how the raw materials affect the finish product's performance.

Because raw materials account for much product variability, any quality-by-design project must define the materials properly. "A wise producer will obviously look at their raw material above and beyond pharmacopoeial specifications. Until we fully understand, raw material impact, which is what FDA is driving us to, we'll have somewhat of a hit or miss approach," says Carlin.

Research and education are key. The National Institute for Pharmaceutical Technology and Education (NIPTE) is one organization that is taking a proactive effort in trying to increase the scientific understanding and correlation between the physical and mechanical properties of materials and their functionality. NIPTE is a consortium of 11 university members and has a formal agreement of collaboration with the FDA. NIPTE is seeking opportunities to work with the pharmaceutical industry and other organizations such as the USP, IPEC, and NIST to develop the basic science of pharmaceutical development and manufacturing. It

is in the process of registering as a non-profit organization and is currently seeking funding from the federal government. When NIPTE obtains federal funding, it plans to fund research in functionality characterization. "What needs to happen first is to understand which properties are important, we have to have standardized methods so that we can all talk in the same language, and then form an understanding of how these properties affects the functional behavior, functionalities. We will decide which physical and mechanical properties are important, which are more indicative of these functional properties and behavior," says NIPTE's executive director Prabir Basu.

Changes in some pharmacy-school curricula also could help formulators understand material properties better. "Pharmacy schools used to teach a lot of bench preparations such as how to dilute powders. Formulators don't get that training now," says Moreton. "They don't get the chemical background, and most pharmaceutical engineering courses really don't touch the chemistry. They touch the mechanical engineering part of it, and they ignore the chemistry of the active drug. Formulators need training in organic chemistry; they need training in properties of materials, powder materials especially."

These points are important because many in the industry believe the real responsibility for understanding the functionality of the excipient as it relates to the final formulation lies with formulators. "When they are formulating the product in the beginning, they need to do more research to figure out the prop-

erties that they really need to make it work," says Schoneker. This approach will meet some resistance from those who perceive it as another way to add more time-consuming work up front. "But I think the real way to look at it is from a quality by design standpoint: As you understand these interactions between materials and processes in the beginning, ultimately it is going to give you a much better system as you go forward with the ability to make changes much more easily."

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