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EXCIPIENT UPDATE



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21st Century Pharmaceutical Quality: Are We There Yet?

Industry experts tackle sourcing and processing at the upcoming ExcipientFest® Americas Conference

By: **Cindy H. Dubin, Contributor**

Throughout the past decade, there has been an improved understanding about the importance of excipients: a better understanding of their functionality, how they are made, and how they affect where they are used. No longer are they just a commodity. The proof is in what some claim is a \$2.5-billion industry. It is now well established that excipients contribute critically toward processing, stability, safety, and performance of solid dosage forms.

Getting to this point has not been easy. Shifts in purchasing decisions, a lack of understanding about how excipients impact drug performance, and poor quality excipients, have littered the path. Now, issues like Quality by Design (QbD), better sourcing strategies, and the use of co-processed excipients are helping to drive the excipient industry, and these are just some of the topics expected to draw large audiences at this year's ExcipientFest Americas® 2009 (April 22-23, Puerto Rico).

WHEREIN LIES THE POWER?

Imagine a time when formulators were actually on a first-name basis with their excipient supplier. Imagine a time when there was no second-guessing the quality of those excipients. Imagine a time when pharma companies were intimately familiar with the manufacturing process of the excipients.

That time ended about 10 years ago when excipient purchasing decisions fell out of formulators' hands and into those of purchasing agents. Their directive is simple: Get the ingredients at the lowest price. Driven by this motto, their quest can take them literally anywhere in the world. There is little effort spent on learning about the history of the company making the excipients, the manufacturing process,

or the quality of the ingredient.

"The origin and grade of excipients to be used in a drug product are often chosen by supply chain people, and they are basically telling formulators what excipients they should use - a decision sometimes based solely on price," says Dave Schoneker, former IPEC Americas Chair, and Director of Global Regulatory Affairs at Colorcon, who will present *Risk Mitigation Strategies in Excipient Sourcing - IPEC's View on the Coming Legislative and Regulatory Changes* at ExcipientFest Americas.

The path that some purchasing folks are going down is opening pharma companies up to potential trouble. The compositional make-up of the product from a new supplier might be different than the same excipient from the known supplier who has historically been used.

"Once the purchasing folks believe that they can get a cheaper price, they don't always do what is necessary to mitigate the potential risks," says Mr. Schoneker. "Some pharma companies have great programs in place, which fully assess quality as well as cost, but some do not. Poor-quality excipients can cause death, and have in a number of cases, during the past few years."

He says Big Pharma and generics should all use improved auditing programs to ensure the quality of any alternative excipients they plan to use. "Many companies will have audits in place for the top 10% to 20% of suppliers they buy from most, but not necessarily for the less-used suppliers," he says.

Audits should include visiting the supplier's site, understanding manufacturing controls, and making sure the product is made to pharmaceutical-grade standards. This puts pharma in a position of knowledge. "This is necessary because the pharmaceutical user is ultimately always responsible for the quality of the excipients that go into a drug product."

When problems do arise with the use of an excipient in a drug product, Mr. Schoneker says typically, pharma is primarily responsible, not the excipient supplier. "In some cases, the excipient manufacturers do not even know that the excipients they are selling will be used in drug products. Many times, there is a lack of communication between the user and the maker about how an excipient is to be used." This, he says, has caused many problems in the past.

"Impurities in industrial-grade excipients are different than in pharmaceutical grade," says Mr. Schoneker. "If the excipients are purposely adulterated, that's criminal, but if the supplier is unaware of how their product will be used, they may not realize the impact of certain manufacturing practices, which could be a problem for certain drug applications. When it comes to the use of lower-quality excipients in drug applications, if there is a willing buyer, there will always be a willing seller."

"Many in the industry have what I call Desired Outcome Syndrome (DOS)," continues Mr. Schoneker. "They want something so badly, they convince themselves it's right. Their control system really has holes in it, but they are certain the cheap excipients are good. Their vision becomes cloudy. As stated earlier, at the end of the day, the responsibility fully lies with pharma. They made the decision to use the alternative material; therefore, they are accountable. The FDA believes this 100%."

The International Pharmaceutical Excipients Council (IPEC) is trying to develop a third-party certification process of excipient suppliers. The goal is to cost effectively share these reports with industry so that anyone purchasing from these alternate suppliers can have access to the results at a low cost.

This past September, IPEC released its newest guide on excipient quality,

offering guidance to suppliers on how to market their product to pharma, how pharma can select the right excipient for specific intended use, and how to improve the communication between maker, distributor, and user. IPEC has also developed a new division, the International Pharmaceutical Excipients Auditing, Inc., to provide third-party auditing services of excipient manufacturers and distributors.

Federal regulators are also taking steps to facilitate the communication process. The Food and Drug Administration Globalization Act of 2009 has language that proposes country-of-origin labeling and a registration fee to cover the cost of drug product and ingredient inspections. The draft also proposes to increase the capacity of FDA to monitor foreign facilities.

Additionally, the draft Drug and Device Accountability of 2009 aims to ensure the identity and source of drug ingredients. This would involve various methodologies, giving manufacturers responsibility for the quality of their drug ingredients, and ensuring adherence to GMPs.

"The goal of all of these regulatory steps is to define what is good enough for pharmaceutical uses," says Mr. Schoneker.

And industry is looking forward to formulators and developers playing a greater role in excipient acquisition in the future. "The gatekeepers we've come to know will diminish in this economic climate as pharmaceutical companies strive to create their next blockbusters," says Alen Guy, PhD, Director of Business Development, Balchem Encapsulates. "This can only be done by producing better product and better dosage forms with quality excipients."

CO-PROCESSING & QbD

Overall quality of a finished product depends not only on the active ingredient but on the excipient and manufacturing as well, so it is extremely critical that formulators can guarantee the safety and quality of the ingredients being used in drug design.

"We have seen an integration of Quality by Design (QbD) and supply chain security, making sure the excipients purchased are safe and have the greatest impact on the attributes that affect drug release," says Mr. Schoneker.

"Quality by Design is "hot" right now and plays two very important roles. First, it ensures a consistent, robust pharmaceutical manufacturing process from preclinical to post-launch. Product performance will be the same every time," says Dr. Guy, who will present *Co-Processed or Pre-Processed: Highly Functional or Convenient Excipients*

at the upcoming ExcipientFest Americas conference. "Second, the design and formulation serve a purpose, and there is more flexibility with the design of the dosage."

Designing excipients specifically for QbD is attracting industry interest. These are called co-processed excipients: two or more excipients specially processed together to interact with each other at the sub-particle level, to minimize the variability of individual excipients, and to enhance their performance. This enhanced functionality would not normally be achieved by merely blending the excipients, explains Dr. Guy.

Major players in the market include JRS Pharma, BASF Corporation, Colorcon, and SPI Pharma. Up-and-coming players are Fuji Health Sciences and Mallinckrodt Baker. "This represents a rapidly growing market within the excipient industry with an increasing number of product launches and new IP being generated annually," says Dr. Guy. He estimates the co-processed excipients market for use in solid-dose forms to be around \$30 million a year.

Excipient mixtures in co-processing are produced to make use of the advantages of each component and potentially to overcome their individual disadvantages. They are meant to enhance functionality and make a more consistent product. A significant number of co-processed excipients are specifically designed for use in a small set of circumstances, such as for orally disintegrating tablet forms.

"This trend has risen out of the pharma industry's need to enhance brand lifecycle and produce dosage forms that improve patient compliance with their prescription," says Dr. Guy. Presently, only a small number of co-processed excipients are aimed at more general formulation applications.

The individual identity of the excipient is not compromised in the process. "This is key to demonstrating that a new compound has not been developed," says Dr. Guy. "That would be a negative outcome as the material would need to undergo toxicity evaluation, normally an expensive process."

The actual process of combining the excipients is critical to their performance. Dr. Guy says if they are not processed the right way, they won't offer very much advantage. "As a matter of fact, a co-processed excipient can be reduced in functionality if the process is not correct."

Direct compression, wet granulation, and spray drying all have a place in producing co-processed excipients, but knowing which to choose will make all the difference in product stability and quality. "Often, we see companies make processing choices based on risk," says Dr. Guy. "Ultimately, they wind up with a suboptimal

process. The point is to co-process, not conveniently blend just to save money and reduce risk."

While the benefits of co-processed excipients are numerous - reduced number and level of excipients, increased manufacturing throughputs, improved consistency, and increased robustness - industry regulators are slow in accepting them. There is a lack of USP monograph support, and until monographs are developed, industry will not accept or invest in co-processed excipients, believes Dr. Guy. "Monographs are everything for many pharma industry gatekeepers." This means complexity for a pharma company trying to get a drug approved that exhibits co-processed excipients. "If a company can't cite a monograph, the regulatory work won't go away," says Dr. Guy.

"Until the FDA, industry and USP agree that co-processed excipients are here to stay, they won't become mainstream," he says. "Once they do become mainstream, and a framework is developed, critical mass will build up. It is sound business practice to convert to them if they are better."

There is also that little matter of price. Mr. Schoneker says the cost of quality co-processed excipients might be more, but their performance more than makes up for it.

"Quality excipients are more expensive, but pharma needs to pay for them," says Dr. Guy. "It means investing in a space many don't consider worth investing in. There needs to be a better understanding of the existing excipient base to innovate and take science further, and provide dosage forms that not only fit the QbD requirements as the pharma industry understands them, but also the consumers' needs to have medicines they can take easily. Innovation leads to better performance. The goal is 21st century pharmaceutical quality." ♦

About ExcipientFest® Americas: *This year, ExcipientFest Americas® will be held April 22-23 in the Grand Ballroom at the Puerto Rico Convention Center in San Juan, Puerto Rico. In addition to the content presented in this article, attendees can visit sourcing and science programs discussing IPEC's Recent Activities, Chemistry 101 for Non-Chemists, Managing Material Supply, Supplier Relationship Management, Dynamics of Film Coating, Understanding Drug-Excipient Interactions, SUPAC, Improving Solubility of Poorly Soluble Drugs, and many more. Attendees will have the opportunity to visit with excipient manufacturers and suppliers on the expo floor. Please visit www.excipientfest.com for more information.*