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## Big Pharma and Suppliers Collaborate on Excipient Quality

Topic takes center stage at upcoming ExcipientFest® Americas conference

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Drug Delivery  
Technology

As appeared in

### Introduction

Panama, 2006: 21 people die after taking a government-made cough syrup contaminated with diethylene glycol that had been mislabeled as USP-grade glycerin, a widely used excipient. Another 38 people were affected by side effects, including disorientation and kidney failure.

Haiti, 1996: glycerine contaminated with diethylene glycol killed 88 people.

India and Bangladesh, 1990–1992: paracetamol (acetaminophen) syrup contaminated with diethylene glycol from propylene glycol led to 236 deaths.

Nigeria, 1990: 47 people die after taking cough syrup contaminated with solvents.

“In these cases, the fraud was deliberate where the material was mislabeled for pharmaceutical use,” says Chris Moreton, PhD, a partner with FinnBrit Consulting in Waltham, MA. “The people accepted the material on the basis of a certificate of analysis (CoA). The ID test in both 1996 and 2006 may not have picked it up. FDA has since mandated changes and there is now a test for absence of DEG in the USP monograph for glycerin.”

Dr. Moreton, who will present “Excipient Sourcing in a Global Market: How to avoid another Panama” at the upcoming ExcipientFest® Americas annual conference and pharmaceutical expo in Puerto Rico (April 16–18), says that the events such as those above are not just happening in developing countries. He will discuss what is being done to make it more difficult for these incidents to occur. Earlier 2007, several countries – including the US – issued a major recall of toothpaste made in China because it contained diethylene glycol that had again been mislabeled as glycerine.

“Situations like this are not widespread, but it is the incident not discovered that causes concern,” says Bill Webb, Director of Quality, Eurand in Vandalia, OH, who will discuss “Excipient Qualification Process Used by Pharma Companies—A Comparison vs. FDA Requirement” at ExcipientFest Americas. He will describe the quality challenges that suppliers face and how to be successful by working with Big Pharma. “We don’t know when the next event is going to hit.”

Mr. Webb and Dr. Moreton agree that such incidents occur because of rogue individuals who deliberately commit fraud, not the industry as a whole. Both concur that Big Pharma and excipient suppliers must work together to ensure the quality of excipients.

ExcipientFest is helping to set standards of excellence by educating suppliers about GMP compliance and helping them interpret regulatory standards.

### A Bright Future for Excipients

There is opportunity for suppliers to be successful, says Mr. Webb. And the market for excipients substantiates that statement. Collectively, these materials accounted for a \$3.5B global market in 2006, according to Massachusetts, US-based market research firm BCC Research, which recently published the report, Excipients in Pharmaceuticals. BCC sees the market growing at an average rate of 3.8% per year to \$4.3B in 2011.

Growth opportunities will extend to a range of compounds and applications, according to a January 2008 report available at reportlinker.com. Based on advances in material quality and processing safety, gelatin will remain the dominant compound for drug encapsulation, warding off challenges from more expensive cellulosic and vegetable oil derivatives. Due to the breadth of existing and potential applications in drug formulations and delivery systems, cellulose derivatives will eventually evolve into the top-selling group of pharmaceutical excipients, according to the report, US Excipients Market. These compounds will command especially strong growth opportunities as controlled release agents and in specialty uses such as enteric coatings and chewable tablets. Additionally, ongoing efforts to improve the bioavailability and safety of parenteral and inhalation drugs will boost demand for specialty polymer excipients, especially compounds with sustained-release and targeting properties. Multifunctional synthetic polymers, such as povidone, will broaden applications in high value-added oral medicines, including disintegrating tablets and controlled-release drug delivery systems.

Cost and quality advantages will also expand market opportunities for starch-based excipients, with pregelatinized starch fillers and binders, and sodium starch glycolate disintegrants commanding the best sales growth. Based on ease of processing advantages and good compacting and compression properties, lactose will retain widespread use as a tablet filler and diluent. Sorbitol and mannitol will see the strongest demand growth among polyol excipients, according to the report, the former from uses as a liquid drug diluent; the latter from applications as a diluent in parenteral preparations. Sterile water will increase with upward trends in developing parenteral drugs, especially recombinant DNA and monoclonal antibody preparations.

Finally, efforts to reduce drug dispensing errors and strengthen drug anti-counterfeiting safeguards will prompt drug manufacturers to use FD&C colors and specialty ink excipients.

### Final Blame Lies With Big Pharma

The increase in fraud-deterrent use of excipients reflects Big Pharma’s understanding of

the ultimate responsibility it has in ensuring excipient quality. “In my opinion, the ultimate responsibility lies with the product license holder; the people selling the finished product,” says Dr. Moreton.

Mr. Webb agrees: “The finished product manufacturer is responsible for its drug product.”

Using excipients that deter fraud is only one way that Big Pharma can take control of the situation. Drug manufacturers must play a much more active role in staying in close communication with excipient suppliers. “We can no longer use the model we used 20 years ago for dealing with suppliers,” says Mr. Webb. “Auditing suppliers every two to four years has fallen by the wayside. If a drug manufacturer suspects quality issues early on, there is a good chance that the supplier can respond quickly and the problem can be resolved.”

While suppliers should have an established quality system and comply with that program, Big Pharma should be focused on what makes that supplier acceptable to do business with, and have SOPs in place for making that determination. Mr. Webb says that all of this is not say that Big Pharma has to hold the hands of its suppliers or be overly authoritative, but suppliers should recognize the opportunity they have to be successful by changing their business models to be in closer contact with pharma. “This does not have to be a contentious relationship at all,” says Dr. Moreton, “just a continuing dialogue between supplier and purchaser.”

Dr. Nick Buhay, Acting Director, Division of Manufacturing and Product Quality, Office of Compliance, Center for Drug Evaluation and Research (CDER), FDA, says drug manufacturers should have the following elements in place to ensure excipient quality:

- Specification development based on critical quality attributes;
- Process controls that ensure consistent conformance with specifications;
- Assurance that every batch is tested to ensure conformance with all requirements for conformity with written specifications for purity, strength and quality (Note: drug manufacturers can rely on suppliers for this testing, provided that the reliability of the suppliers’ test results is validated at appropriate intervals); and
- SOPs detailing a scientifically sound approach to ensure periodic validation of suppliers’ test results.

“For excipients that are critical to the quality of the finished dosage form, testing by the drug product manufacturer may be necessary to verify the critical attributes of every batch,” says Dr. Buhay.

## Building a Better Fence

Most certainly included in that dialogue will be how to comply with industry guidelines on excipient quality, and even with which guidelines to comply. The International Pharmaceutical Excipients Council (IPEC) “is working to ensure the flow of safe, useful excipients to ensure safe and effective finished prescription and OTC drug dosage forms in the international marketplace.” IPEC-Americas’ guidelines are being harmonized with those of IPEC Europe and Japan (JPEC). This, says Dr. Moreton, is helping direct Big Pharma as it communicates with excipient suppliers.

Additionally, last year, the Bush Administration put together a task force, the Interagency Working Group on Import Safety, headed by the secretary of Health and Human Services. In November 2007, the group presented an Action Plan to the President, which contained 14 broad recommendations and 50 action steps that provide a road map for better protecting American consumers and enhancing the safety of the increasing volume of imports entering the US. Additionally, under the Plan, FDA should have the authority to require producers of certain products to certify that their good meets FDA standards in order to export to the US.

Mr. Webb says that part of FDA’s work will include establishing a presence in China and some of the other countries mentioned earlier. “China is a big trading partner with the US and it does have an initiative to improve its pharmaceutical infrastructure. There are companies over there that are trying to get on this bandwagon, but they are not well trained. FDA will work to raise awareness and the bar to weed out bad practices.”

FDA’s involvement is helping to elevate the importance of excipients in formulation.

“Quality characteristics of excipients are significant to the overall quality of the drug products in which they are used,” states Dr. Buhay.

That significance makes it even more critical for greater control over their quality. Mr. Webb says: “Pharma and suppliers are recognizing that excipients are being elevated in importance by FDA and the recognize the need to be partners in order to move the industry forward and protect the safety of the consumer.”

“The ultimate goal is to get the small-guy offenders that tend to fly under the radar,” says Dr. Moreton. “But don’t expect any one set of standards to be totally effective,” says Dr. Moreton. “A series of standards is needed to build a better fence.”

## The Cost of Compliance

There is a cost to build that fence for both the auditor and the audited. If the pharma company performs the audits in-house, then an amortized cost of about \$5,000 audit in the US can be expected, says Dr. Moreton. This includes salary and payroll costs as well as travel costs. The cost of overseas audits will be higher, up to \$10,000, depending on where the site is located.

The costs to the manufacturer/supplier are less, heavy on time (man hours); probably costing about \$2-3,000 per audit day. The costs mainly arise because the audit takes staff away from their other duties.

If third-party audits were acceptable, and the International Pharmaceutical Excipients Auditing, Inc. (IPEA) scheme or something similar could be used, then the costs mentioned above could be less, says Dr. Moreton.

“When you look at how both sides are addressing auditing, you see suppliers moving toward more group audits (multiple customers auditing at the same time), requiring payment for audits by pharma companies and having independent auditing firms perform audits and providing those reports to customers instead of agreeing to an audit by the customer,” says Mr. Webb.

Reluctance on the part of a supplier to host audits is an immediate red flag, continues Mr. Webb. The supplier’s reasons may be valid, but the message that it sent would be of concern. “Once the concern has been created, it may result in the supplier expending additional resources to effectively address those concerns.”

Audits are simply a cost of doing business in the pharmaceutical industry and tend to be accounted for in the budgeting process. We should be asking ourselves: “What is the cost of not doing the audits, and not building the relationships with our customers and suppliers?” says Dr. Moreton. “What is the cost of a 483 citation from the FDA, higher insurance premiums, etc.? What is the cost of a human tragedy, such as Haiti or Panama, happening here in the US?”

“In the past, we have tended to assume that everyone is a nice guy,” continues Dr. Moreton. “Well, recent events have shown us that we cannot assume anything. We have to build bridges to our suppliers and customers, amongst other things, if we are going to maintain the public trust. The public trust of pharma is shaky; we cannot afford to shoot ourselves in the foot over adulterated excipients.”

## About ExcipientFest Americas

*ExcipientFest features in-depth educational sessions & workshops on trends in Excipient Technology, New Drug Applications, Regulatory Issues and Sourcing Strategies. The sessions & workshops have a science focus and are true to the role of functionality of pharma ingredients in the formulation process.*

*The Drug, Chemical & Associated Technologies Association (DCAT) has recently assumed the operation of ExcipientFest Conference and Pharma Expo. A second event, held last year in Ireland is also being operated by DCAT. The programs are now being presented as ExcipientFest Americas in Puerto Rico, where 9 of the world’s 10 most popular drugs are produced; and ExcipientFest Europe.*

*In addition to excipient quality, attendees to ExcipientFest Americas ([www.excipientfest.com](http://www.excipientfest.com)) can attend presentations about SUPAC, Design of Experiments, Film Coating, Tablet Dosage Forms, and of course, visit with excipient manufacturers.*

## Bill Webb



Bill Webb is currently Director of Quality for Eurand, a specialty pharmaceutical company focused on the development of novel drug delivery technologies and products. Mr. Webb joined Eurand in

2000 and is responsible for Eurand, Inc. U.S. Quality Function and has performed audits and vendor qualifications in the U.S., Europe, and Asia. He provides direction and leadership to Eurand U.S. Quality and Operations staff and also sets and maintains quality systems and procedures to assure conformance with all current Good Manufacturing Practices administered by FDA, MHRA, Italian Authorities and other regulatory authorities.

Prior to joining Eurand, Mr. Webb was the Quality Assurance Supervisor at Forest Pharmaceuticals, Inc., where he was responsible for the similar functions that he has been maintaining at Eurand Inc. In addition, Mr. Webb has served as Quality Assurance Coordinator and Quality Control Inspector and has continued to advance in his field combining compliance responsibilities with work in Drug Enforcements Agency compliance and the Federal Drug Administration regulations. Mr. Webb has over 24 years of experience in the pharmaceutical industry in the Quality Department.

## R. Christian Moreton PhD



Dr. Moreton received his B.Pharm degree from the University of Nottingham, UK, his M.Sc degree from the University of Strathclyde, UK and his PhD from the University of Wales, Cardiff, UK.

He is a registered Pharmacist in the UK. Dr. Moreton has over thirty years’ experience in the pharmaceutical industry. He has worked as a formulation scientist developing a variety of different dosage forms, and also in QA/QC and Technical Support in excipients and drug delivery. Prior to starting FinnBrit Consulting, Dr. Moreton was most recently Vice President, Pharmaceutical Sciences at Idenix Pharmaceuticals, Cambridge, MA where he was responsible for the design, development, scale-up, technical transfer and validation of all drug products and associated analytical methods, both during clinical development and eventual transfer into commercial manufacture, working with licensing partners and contractors.

Dr. Moreton is a member of the Board of IPEA, Inc. He is a past chair of the AAPS Excipients Focus Group and a past Chair of IPEC-Americas, and still active on several IPEC committees including GMP, QbD and Excipient Composition. He is a member of the International Steering Committee of the Handbook of Pharmaceutical Excipients, a member of the Editorial Advisory Board of Pharmaceutical Technology, and a member of the USP Expert Committee—Excipient Monograph Content 2. He has authored and co-authored scientific papers and book chapters, and lectured extensively in the areas of excipients, drug delivery and formulation at universities, training courses and symposia in the US and Europe.

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