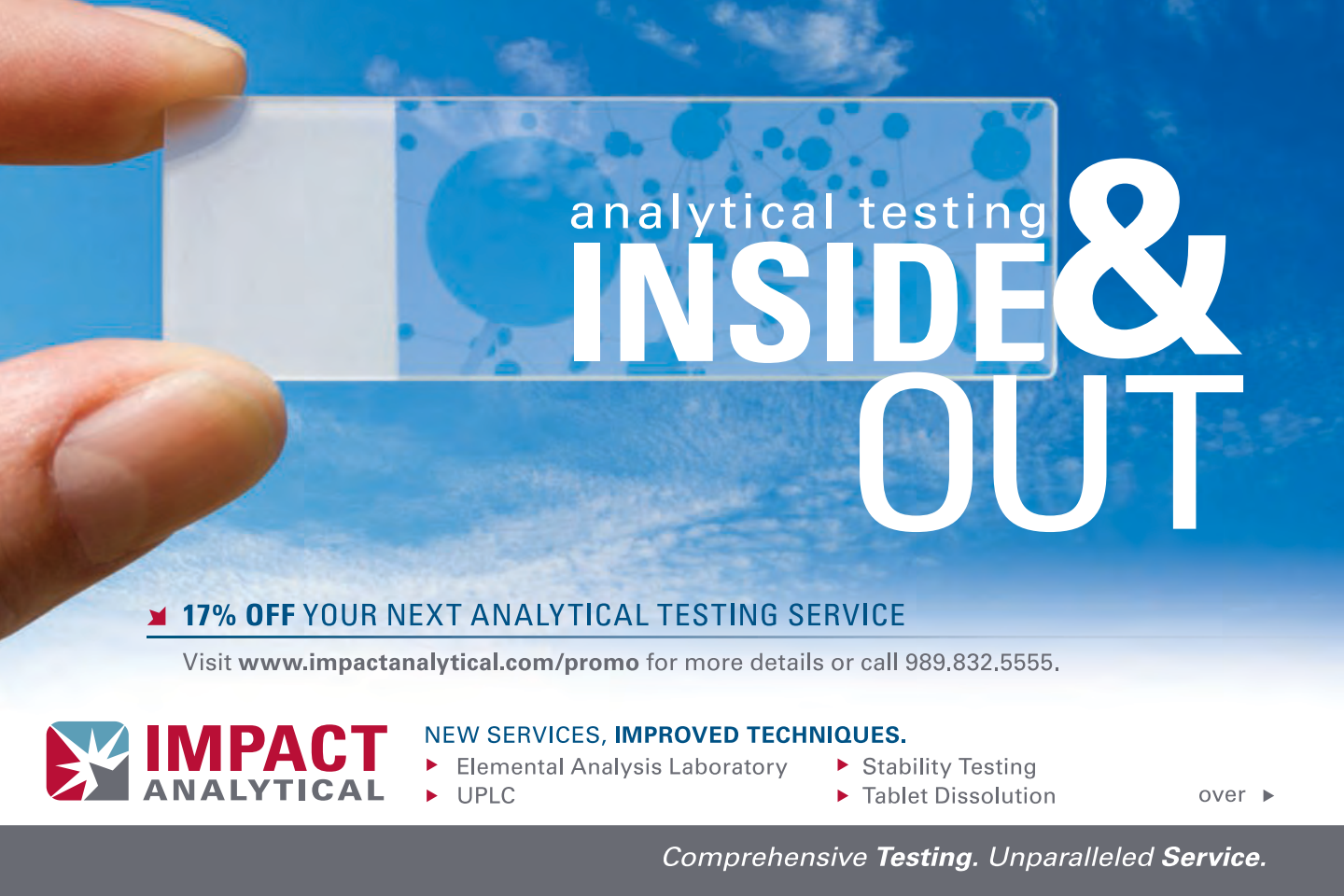
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Addressing Segregation of a Low-Dosage Direct Blend

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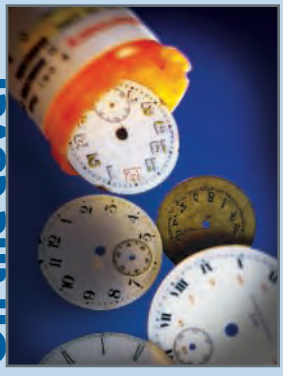
On the cover



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### Issue extras

- An expanded version of this month's cover story provides input on the practicalities of real time release testing from experts at Freeman Technology, GE Analytical Instruments, Malvern Instruments, Mettler-Toledo AutoChem, and Real Time Analyzers.
*Q&As moderated by Angie Drakulich*
- An expanded version of this month's Packaging forum includes cold-chain guidelines.

### Web exclusive

- FDA Obtains Full PIC/S Membership in 2011, a perspective from *Thomas Peither.*

### eNewsletters

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- *Sourcing and Management:* The February edition includes an Informex preview.
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### Supplement

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# Follow-Ons: The New Black?

**Michelle Hoffman**

## Follow-ons were all the rage at this year's JP Morgan Healthcare Conference.

Every January, the movers and shakers of the pharmaceutical industry convene in San Francisco for JP Morgan's annual Healthcare Conference. There, the pharma industry's corporate leaders articulate their business strategies before an audience of investors and analysts. The emerging themes define strategic trends for the coming year, much as fashion trends are set during New York Fashion week. So what's the vogue in pharma for 2011? It looks as though follow-on biologics are the new black.

News stories coming out of the conference reported how one pharma major after another announced plans to get into follow-ons, a surprising move for companies that, until now, based their reputations on innovation and not imitation. Maybe it shouldn't come as a great surprise, however, considering that recent technical innovations and regulatory advances are creating fertile ground for follow-on commercialization.

New analytics are making it possible (or will soon make it possible) to characterize proteins as they're being synthesized in the bioreactor. Advances in chromatography and mass spectroscopy allow manufacturers to detect variations in amino acids and glycan disposition within protein products that might alter their biophysical properties.

The regulatory agencies are also advancing guidances for commercialization of complex biosimilar molecules, such as monoclonal antibodies (mAbs). But as the US pharma majors state their interest in biosimilars, it's important to note that US regulations lag behind Europe. Whereas the US held its first hearing on regulations for follow-ons in November 2010, the European Medicines Agency (EMA) had already developed a regulatory framework for follow-ons in 2003 and issued its first guidelines in 2005.

**In light of pharma's intent, pressure is on regulators to get up to speed quickly.**

To be accurate, the medicines actually manufactured under the 2005 EMA guidelines are small, very well characterized molecules, such as recombinant human insulin. Recent debates on both sides of the Atlantic center on what constitutes proof of similarity for larger, complex biomolecules.

With the November 2010 release of two draft guidelines, one on similar biological medicinal products containing monoclonal antibodies, and the other on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use, EMA once again leads the way. The focus of the "biosimilarity exercise," notes the guideline on similar biological medicinal products, "is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se, which has already been established by the reference product." And the tests EMA asks for—both *in vivo* and *in vitro*—are aimed at determining "all functional aspects of the mAb even though some may not be considered necessary for the mode of action in the clinic."

Together, the two guidelines ask manufacturers to evaluate differences between innovator and follow-on mAbs in process-related impurities due to differences in expression systems used by different manufacturers. They also address "less well characterized" impurities, differences in formulation, unusual excipients, post-translational modifications that can affect the conformation, aggregation, and ultimately the immunogenicity of the follow-on product. The guidelines go on to outline tests for pharmacodynamics, immunogenicity, and suggest an overall risk-based approach to follow-on mAb manufacturing.

Should EMA enact these regulations before FDA, which seems likely, European Union manufacturers will get a head start over their US counterparts in producing, testing, and marketing the follow-ons, which experience could put firms seeking to do business in the US at a competitive disadvantage in what promises to be a tight and competitive market. In light of pharma's expressed intent to manufacture follow-ons, the pressure is on regulators to get up to speed quickly—certainly before follow-ons are just so last year. **PT**

**Michelle Hoffman** is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to mhoffman@advanstar.com.

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# Fighting Rogue Pharmacies

Alexis Pellek

## Government and private sector efforts take on counterfeit drugs online.


AUGUST STEIN/PHOTODISC/GETTY IMAGES

How bad is the problem of illegal online pharmacies? One in six Americans has purchased a prescription drug online without a valid prescription, according to research presented by The Partnership at Drugfree.org during the White House Forum on Intellectual Property (IP) Theft in December 2010. That means 36 million Americans were at risk for buying counterfeit and substandard drugs from rogue pharmacy websites.

Speaking at the forum, US Attorney General Eric Holder noted examples of ways the Department of Justice is working to protect consumer health and safety, including the prosecution of counterfeit traffickers, the seizure of more than 80 websites selling counterfeit goods, and the use of new technologies and public-education campaigns. He called for more cooperation between government agencies, foreign regulators, and industry, saying, "The Internet remains a haven for illegal pharmacies and other operations that pose a danger to the American people, and we need a concerted, collaborative effort to put these illegal operations out of business."

A voluntary partnership made up of Google, Microsoft, and several other companies will target illegal online pharmacies and work to stop the sale of fake drugs. Along with American Express, eNom, GoDaddy, MasterCard, Neustar, Network Solutions, PayPal, Visa and Yahoo!, the companies agreed to form a nonprofit organization focused on fighting the spread of counterfeit drugs on the Internet by eradicating rogue pharmacies.

For a related story, see this month's Viewpoint column on illegal drug reimportation on p. 98. **PT**



**Alexis Pellek** is an assistant editor of *Pharmaceutical Technology*.

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# Looking in All the Right Places


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**Cautionary Tales from the Files of "Control," a Senior Compliance Officer**

## Taking care to note, file, and re-check information can save one from future mishaps.

### It's de nature of the thing

"We bought a product that was made in the US, and are moving it to our European manufacturing site," reported our GMP Agent-In-Place. "Because we make a similar product, we assumed it wouldn't be much different. However, one of the processing aids for the new US-based product was denatured alcohol. We replicated the processing aid with local-source denatured alcohol rather than paying to transport US-manufactured alcohol (not to mention dealing with the cross-border alcohol laws).

"It turns out," our agent continued, "US denatured alcohol (3A) uses methanol as a denaturing agent. Our local denatured alcohol uses methyl-ethyl-ketone, and this made a big difference in the final product. The ketone was concentrated with the product during processing, rather than being washed off in the purification process as was the methanol, so the first test batches were unusable for licensing the new manufacturing site and had to be destroyed."

### Stressed out

"One of our new vessels developed a leak near the bottom," groused our GMP Agent-In-Place. "It took some analysis, but we discovered that the magnetically coupled stirrer slowly stressed the nearby welds, which then cracked and caused the leak. I was proud that we not only fixed the vessel and inspected and reinforced others on the site, but we also made sure that all similar vessels at our other manufacturing sites across the ocean were inspected and reinforced as needed. That's a good preventive and corrective action program in action."

### The dog ate my homework

"One of the products we distribute is manufactured by another firm who also owns the license. However, we do the packaging and labeling," our GMP Agent-In-Place began. "Our contract stated that we needed the other firm's written approval of all labeling and marketing materials. We thought we had a good system for managing this task. However, when the firm asked to see the approval for a particular marketing campaign, no one could find it. The firm is seeking a public repudiation of the advertisements that went out. Our negotiations are still pending."

**The firm is seeking a public repudiation of the advertisements that went out.**

### Repeat performance

"Because I have a lot of experience in hosting FDA inspections and in auditing international sites, I was asked to help prepare our European site for a preapproval inspection," bragged our GMP Agent-In-Place. "I had just begun the preparation when all of the contact personnel were pulled away. The site had a media failure and all available hands were needed to address it and the consequences. Because I had traveled 3000 miles to get there, they provided a junior quality-division employee to walk me through the documents. Ultimately, there was not enough information available without the staff and I had to come back three weeks later."

### Quality?

Over the years, I've had a variety of quality-based initiatives thrown at me (see list below). I'd like to hear your experience with them. Some are so old that I've forgotten what the acronym stands for.

- Cost of quality
- Quality benchmarking
- TQM
- Quality circles
- QPIC
- Paperwork reduction program
- Customer satisfaction program
- TOPs
- Order winners
- C&L reengineering
- President's circle
- Circle of excellence
- Best practices versus Best practices II
- Global performance improvement initiative.

Send your thoughts to AgentinPlace@advanstar.com. —*Control* **PT**

*Pharmaceutical Technology's* monthly "Agent-in-Place" column distills true-life cautionary tales from the files of Control, a senior compliance officer. If you have a story to share, please email it to Control at AgentinPlace@advanstar.com. We won't use any names, but if we do use your experience in the column, you'll receive a Pharmaceutical Technology t-shirt.

# In the Field

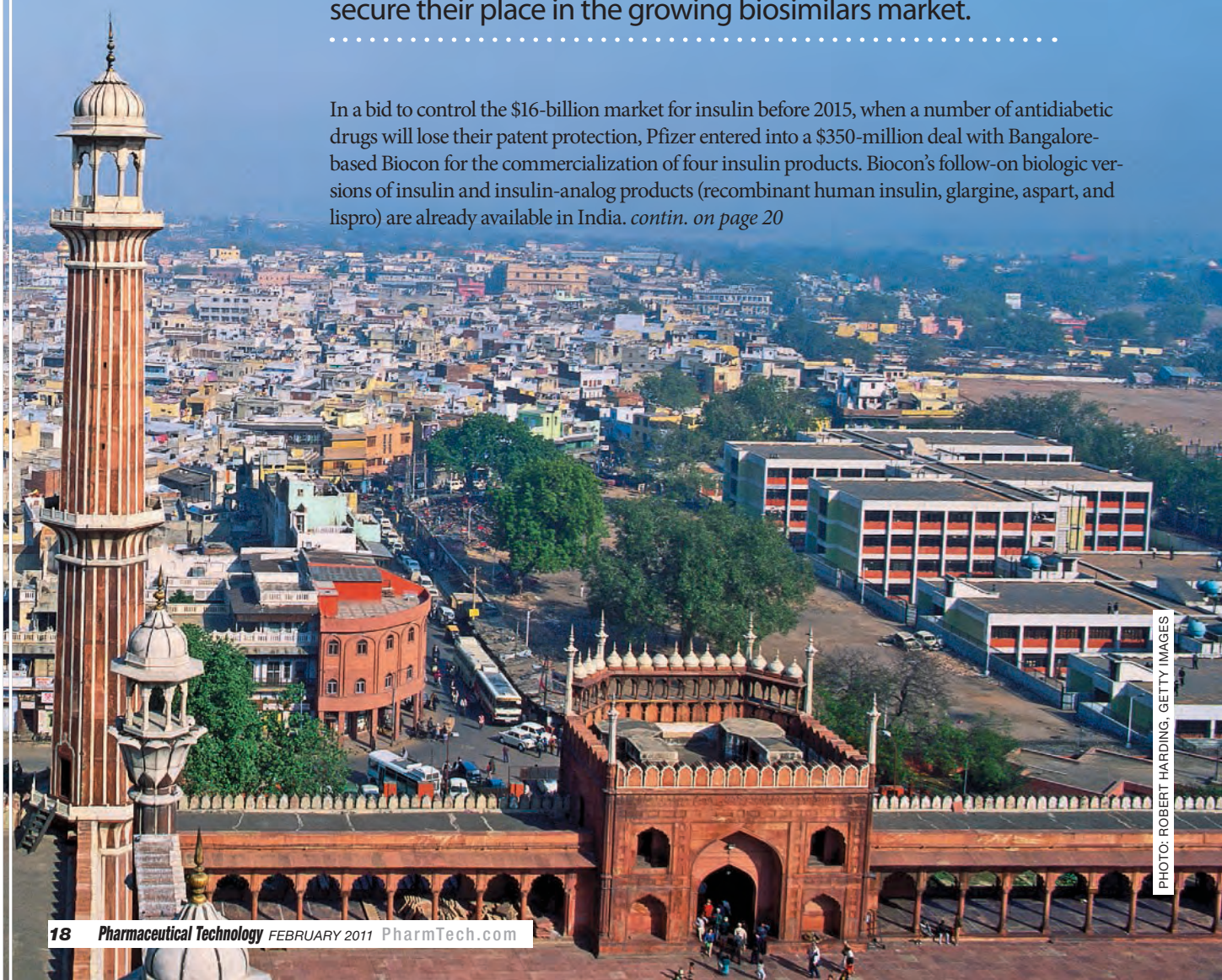


# Report from: India

**A. Nair**

As biologic-drug patents move toward expiration in the US, Indian firms with experience in the follow-on biologics arena are eager to partner with global manufacturers and secure their place in the growing biosimilars market.

In a bid to control the $16-billion market for insulin before 2015, when a number of antidiabetic drugs will lose their patent protection, Pfizer entered into a $350-million deal with Bangalore-based Biocon for the commercialization of four insulin products. Biocon's follow-on biologic versions of insulin and insulin-analog products (recombinant human insulin, glargine, aspart, and lispro) are already available in India. *contin. on page 20*



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*contin. from page 18*

"Our decision was timely," said Biocon Chairperson Kiran Mazumdar Shaw. "Biosimilars are gaining a lot of traction in the United States. The deal will help us emerge stronger in follow-on biologics as well as in the diabetes segment," she said.

**Jumping on the follow-on biologics bandwagon**

Biocon's deal with Pfizer, which closed in October 2010, was just one of the many biotech-based deals that Indian drug manufacturers have been making with Big Pharma companies around the world. Dr. Reddy's Laboratories (Hyderabad), Ranbaxy (Gurgaon), Shantha Biotech (Hyderabad), and Serum Institute (Pune) are actively involved in the follow-on biologic space, and analysts and investment bankers maintain that additional Indian drug companies such as Panacea Biotech (New Delhi), Intas Biopharmaceuticals (Ahmedabad), Reliance Life Sciences (Navi Mumbai), Bharat Biotech (Hyderabad), and Lupin (Mumbai) stand to benefit significantly given their portfolio of biotech drugs.

Tarun Shah, Asia head of Mehta Partners, the strategic business advisor to Japan's Daiichi Sankyo in its 2008 majority stake in Ranbaxy Laboratories, said, "Bringing a biosimilar drug to market is no easy task. It costs 20 times more than [small-molecule] generics." (Of note, Mehta Partners has raised equity for Intas Biopharmaceuticals.)

Dhananjay Patankar, COO of Intas Biopharmaceuticals, however, believes that the entry of Indian follow-on biologics manufacturers into the global market could help to decrease exorbitant healthcare costs, especially in the United States.

Given the mounting pressure from governments and patients' groups to reduce the cost of medicine, biopharmaceutical companies that develop biologic drugs have a lot to offer. Herceptin (trastuzumab), for instance, which is a treatment for some forms of breast cancer, can cost as much as $48,000 for one year's worth of treatment, according to industry sources.

Shah points out that the US patent for rituximab (a monoclonal antibody against the protein CD20, for the treatment of rheumatoid arthritis and non-Hodgkins lymphoma) is due to expire in between 2015 and 2018. The product is marketed as Rituxan/Mabthera by Biogen Idec and Roche, respectively. The patent expiry creates opportunities for follow-on biologics manufacturers such as Intas. California-based Spectrum Pharmaceuticals and Viropro, a biopharmaceutical manufacturer, also teamed up on Jan. 5, 2011, to develop a follow-on version of Roche and Biogen Idec's rituximab. "The deal follows a 2007 agreement with Intas Biopharmaceuticals to become Viropro's second monoclonal antibody contract," explained Shah.

Speaking about a recent survey on Type 2 diabetes patients in the US, he noted that 60% of insulin users surveyed were eager to switch to a less expensive [follow-on] form of insulin as soon as the agent became available.

Dr. Reddy's Laboratories launched at a steep discount its first follow-on biologic product, Grafeel (filgrastim), which is used to treat cancer patients suffering from chemotherapy-induced neutropenia, in 2001, in India and its second, Reditux (rituximab) in April 2007. The latter was similar to Amgen's Neupogen to treat neutropenia, a lack of certain white blood cells caused by cancer or bone marrow transplant. This was followed by a third follow-on product, Cresp (darbepoetin alfa, a modified version of epoetin alfa), which the company touts as the first generic darbepoetin alfa drug in the world, used in the treatment of anemia due to chronic kidney disease.

The company intends to market Reditux in other regions, including the US, upon patent expiry of Amgen's Neupogen, according to a company presentation. Managing Director Satish Reddy said the Cresp launch effectively afforded the firm a sharper edge in marketing to the developed world.

Mumbai-based Cipla is also looking to launch follow-on biologics in the US market. Cipla Chairman Yusuf Hamied says the firm is developing a range of discounted biosimilars. First off the block will be copycat versions of two of Roche's biologics: Avastin (bevacizumab) and Herceptin (trastuzumab), which target the treatment of breast cancer. Third will be a follow-on version of Enbrel (etanercept), a Pfizer/Amgen product that treats rheumatoid arthritis. "These [drugs] are very expensive today. When Cipla launches its biosimilars, these big companies (multinationals) will be forced to pull down their price," says Hamied. Together, the three drugs account for $19 billion in annual revenue.

**Accounting for regulatory delays**

Kamal K. Sharma, managing director of Mumbai-based Lupin, says "Once clarity emerges on the regulatory front, especially in the US, biosimilar drugs could provide a huge potential. However, data exclusivity in the US market [remains] a severe challenge," said. The company expects to launch its first follow-on biologic product in India this year.

According to the research firm Nomura Equity Research, between 2008 and 2015, biopharmaceuticals worth $59 billion are set to lose patent protection globally. From 2012, the follow-on biologics market is expected to add an estimated $10 billion in incremental revenues each year until 2020. In the US, the Congressional Budget Office recently estimated that potential savings on biologic drug products in the US between 2009 and 2014 could

*contin. on page 22*

## CSR and sustainability forum

*Pharmaceutical Technology's Sourcing and Management* eNewsletter provides specialized coverage of the bio/pharmaceutical industry's activities in corporate social responsibility (CSR) and sustainability as well as developments from other business sectors, government organizations, professional, trade, and scientific associations, and nongovernmental organizations. The February issue (available at www.PharmTech.com/PTSM) features:

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# Global Healthcare on the Ground

## USP Helps to Improve Drug Quality in 32 Countries

**Angie Drakulich**

The US Pharmacopeia has been helping to improve the quality of healthcare in developing countries for some time. Its most recent program, supported by the US Agency for International Development (USAID), is called Promoting the Quality of Medicines (PQM).

The five-year program began in 2009 and focuses on improving access to quality medicines for people around the world. PQM picks up, in part, where the pharmacopeia's Drug Quality and Information Program leaves off—that program began in 2000 and ended this past December—with the additional benefit of building national capacity to monitor drug quality from the product's manufacture to the end user.

PQM staffers work with local governments, USAID missions and partners, the World Health Organization, the US Centers for Disease Control and Prevention, and the Global Pharma Health Fund, to advance strategies to improve drug quality and use; to increase access to current, evidence-based drug information; and to provide technical leadership. The program is running in 32 countries, which are based on USAID's list of priority countries across four regions (Africa, Asia, Latin America and the Caribbean, and Europe).

PQM starts by assessing a country's ability to ensure drug quality and thereby, secure the public health. Scientists associated with the program look at things like regulation, registration, laboratory control, and distribution. Once the evaluation is complete, PQM staff members work with policymakers and country authorities to address weaknesses in the drug quality monitoring system.

Because it's hard to monitor and control important information about drug usage as well as on adverse events in the developing world, PQM also works with national authorities to produce workshops on pharmacovigilance. Anticounterfeiting workshops and public awareness campaigns (see www.youtube.com/uspharmacopeia for video demonstrations) are also part of PQM's work.

According to USP, the greatest challenges in improving health outcomes in developing countries are the lack of access to quality assured medicines, the irrational use of life-saving medicines, and the accompanying potential consequences, such as developing resistance to those medicines.

"The lack of adequate pharmaceutical systems to manage the storage and distribution of needed medicines to remote areas in a timely manner impedes their effectiveness in rural settings," says Patrick Lukulay, director of PQM. "In addition to pharmaceutical interventions, hygiene, and nutrition are also critical in effecting positive health outcomes."

Further efforts that would be helpful to address these barriers, says Lukulay, are coordination of donor efforts for maximum impact within countries and a focus on building sustainable country systems.

"Putting effective mechanisms in place increases country capacity to manage pharmaceutical commodities and encourages country ownership of major transformational initiatives," he adds.

*contin. from page 20*

be as high as $25 billion, once a pathway for approval and marketing follow-ons is implemented. The fact is, although some of the drugs targeted for follow-on versions have garnered billions of dollars in sales for the original manufacturers, cashing in for Indian companies would be "no walk in the park," says Cipla's Hamied. Much rests on the implementation of the follow-on biologics pathway in the US.

While the US sorts out its implementation plan, some Indian firms are focusing on Europe in the short term. For example, Biocon's Shaw said the firm is in the process of registering its insulin for the European market and has licensed its G-CSF (granulocyte colony stimulating factor) to a North American firm and to Abraxis BioScience for the European market. Biocon is in the midst of setting up a marketing office in London, making Europe its focus during the next 12 months.

Ranjit Kapadia, vice-president of the institutional research firm HDFC Securities in Mumbai, adds that, because the "US law will take a while to be implemented and could undergo some revisions, Indian companies will not be able to launch their biosimilar anytime soon. And that is why the Biocon deal with Pfizer makes perfect sense. They have sold the rights to Pfizer. Now, Pfizer will have to fight to market their biosimilars in the US, whereas the Indian firm can sit pretty."

*A. Nair is a freelance writer based in Mumbai.*

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# Editors' Picks of Pharmaceutical Science & Technology Innovations

To ensure that a tableting process will be predictable, active ingredients and excipients in powder form must undergo granulation. This process results in granules, which comprise several particles each, and helps personnel produce tablets within the desired specifications. This month's products aid the granulation process in various ways. A vibratory feeder from K-Tron conveys cohesive powders into the granulation process. Oystar's high-shear mixers help ensure uniform blends during the operation. A sensor from Natoli allows personnel to monitor materials as they are granulated.

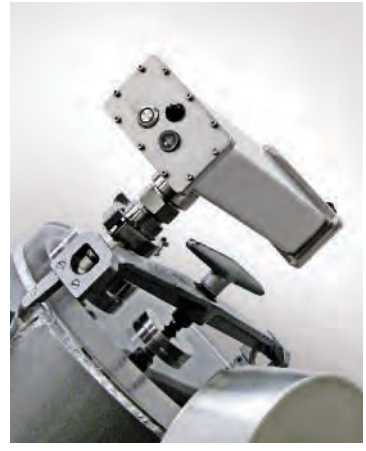
**K-PH-ML-D5-KV2 feeder**
**K-Tron Process Group**
**www.ktron.com**

## Sensor provides speed and sensitivity

The Light-Induced Fluorescence (LIF) sensor from Natoli Engineering is designed to enable real-time monitoring of fluorescent analytes through intrinsic fluorescent sensing in the solid or liquid states. The sensitivity of fluorescence is roughly 1000 times greater than that of absorbance spectroscopy, and the sensor can detect residual active pharmaceutical ingredients (APIs) in rinse water and on surfaces.

The LIF sensor incorporates onboard control sensors, such as reference photodiodes, an accelerometer, a thermal monitor, and various diagnostic tools, that help to provide high-quality data. The device's data output occurs every 100 ms, and this fast response time enables employees to make production decisions.

The LIF Sensor can verify tablets' API content and is suitable for analyzing low-dose, high-potency drugs. Personnel also can use the device to monitor material during granulation, detect the end point of blending operations, and aid in cleaning verification.



**Light-Induced Fluorescence sensor**
**Natoli Engineering**
**www.natoli.com**

## Vibratory feeder conveys cohesive ingredients

The K-PH-ML-D5-KV2 vibratory loss-in-weight feeder from K-Tron Process Group incorporates high-resolution load cells for accurate gravimetric feeding. Typical applications include continuous extrusion, granulation, mixing, and coating. The device's vibratory feeding motion helps convey cohesive powders that may not flow well in screw-feeders, including needle-shaped ingredients and those with high aspect ratios. Users adjust the amplitude of the tray vibration according to the required mass flow through the K-Tron KCM controller, which helps achieve a consistent feed.

## Mixers enable high yields

Oystar Huettlin's HTG and HBG high-shear mixers for wet granulation incorporate a Z-shaped Gentlewing impeller designed to enable fast and uniform mixing. A vertical segment of the impeller reaches from the bottom to the top of the bowl, thus providing a greater granulation area than traditional designs do, according to Nicolas Michel, vice-president of the company's pharmaceutical process division. This design helps increase yields by preventing product from sticking to the vessel walls or lid.

For granulation lines, Oystar links the mixer units to HDGC fluid beds. Process air is forced through radial slots in the fluid bed's discjet, thus setting the product in motion as soon as it is transferred from the mixer. This feature increases material's wall speed and starts the drying process instantly. One of the fluid bed's five independent filters is blown back at any given time, and the unit constantly uses 80% of its maximum filtration area.

**HTG and HBG high-shear mixers**
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# FDA Faces Internal Changes and Challenges on Capitol Hill

**Jill Wechsler**

## Food-safety law, transparency effort, and counterfeit growth will tax agency resources and leadership.

One of the last acts of the 111th US Congress was to approve sweeping food-safety legislation. The new law provides FDA with more authority to recall and monitor food products, boosts its inspection force, and increases its ability to halt unsafe imports. But the law may be the last piece of legislation to expand the agency's authority and resources for some time. With Republicans now holding a majority in the House of Representatives and gaining clout in the Senate, Congress is talking about severe federal budget cuts and curbs on government regulators. New Republican committee chairs in the House are preparing to grill Obama administration officials about the high cost of healthcare reform and antibusiness regulatory policies. A clear target is the slow-down in new drug approvals at FDA and the agency's difficulties in keeping violative products off the market.

In fact, there's strong speculation that Republicans won't provide the $1.4 billion over five years (part of the approved food-safety bill) needed to hire some 2000 additional FDA inspectors to expand the agency's oversight of food growers and processors. Even without a budget increase, the new legislation authorizes FDA to mandate recalls, require food companies to assess risks, and establish new rules for food importers. But it's unlikely that a similar drug-safety measure sponsored by House Democrats will gain traction on Capitol Hill in the coming year. Former House Energy & Commerce Committee Chairman John Dingell (D-MI) has long backed legislation that gives FDA additional enforcement tools over drugs, including mandatory recall authority, more stiff civil and criminal penalties, and authority to subpoena manufacturer records. As with the food safety-bill, Dingell's measure would increase foreign and domestic inspections, strengthen import controls, and enhance plant registration requirements. The best chance of action won't arise until 2012 when Congress has to enact legislation to renew the prescription-drug user-fee program.

### Probing FDA

Meanwhile, FDA and other federal regulatory agencies face a hostile Congress. The new chairman of the House Committee on Oversight and Government Reform, Darrell Issa (R-CA), considers FDA a "broken bureaucracy" according to his website, and has included the agency on his investigation hit-list. Issa was highly critical of agency officials and pharma executives at hearings before his committee last year on delays in drug recalls by Johnson & Johnson's (J&J) McNeil Consumer Products unit. Now as panel chairman, Issa plans to hold FDA officials accountable for such regulatory lapses. In December 2010, Issa sent FDA Commissioner Margaret Hamburg a letter questioning the agency's oversight of a J&J contract manufacturer—and of contract drug-manufacturing practices in general. Issa also will have an eye on how FDA implements the new food-safety law and its growing involvement in tobacco regulation. The agency's Office of Criminal Investigations (OCI) may draw scrutiny following strong criticism last year by Congress' Government Accountability Office (GAO).

Similarly, House Energy and Commerce (E&C) Committee Chairman Fred Upton (R-MI) plans to probe the costs and impact of the administration's healthcare reform legislation, along with what he calls on his website "job-killing regulations" that block technological innovation and wasteful programs that warrant budget cuts. FDA programs and policies will be fodder for the E&C health subcommittee, which is headed by Reps. Joe Pitts (R-PA) and Mike Burgess (R-TX). In addition, the E&C subcommittee on oversight and investigations, now under Chairman Cliff Stearns (R-FL), may continue to analyze drug regulatory problems, such as FDA's handling of heparin contamina-

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### In Washington this month

- New Congressional leadership is set to probe FDA oversight and weaknesses.
- Sharfstein departs FDA after unveiling additional transparency policies.
- FDA is involved in Obama administration efforts to curb drug counterfeiting.

tion and its failure to adequately monitor foreign drug production.

### Deputy departs

At last year's House Oversight Committee hearings on J&J's manufacturing problems and recalls, FDA was represented by Principal Deputy Commissioner Joshua Sharfstein. He won plaudits for having command of the issues and for answering questions directly, a performance that benefited from earlier experience on Capitol Hill as an aide to Rep. Henry Waxman (D-CA). Now someone else at FDA will have to fill the hot seat at Congressional hearings following Sharfstein's surprise departure from the agency last month.

Sharfstein was lured away by an offer to head Maryland's health department, a move that capitalizes on his public health roots as Baltimore's health commissioner before coming to FDA. In moving to the state agency, Sharfstein will manage a $7-billion budget—which is much bigger than FDA's. He also will be involved with implementing the many healthcare-reform programs and policies that require state involvement, including an expansion in Medicaid and formation of new health insurance exchanges.

At FDA, Sharfstein helped to engineer a get-tough compliance policy designed to eliminate perceptions that FDA had become too cozy with industry. This stronger enforcement stance has produced more Warning Letters that cite manufacturing and marketing violations and more criminal investigations, trends that are likely to continue. He also was involved in strengthening FDA's medical-device regulatory process, a high-profile exercise that is still ongoing, and he was a strong advocate for ensuring drug safety and establishing tight curbs on the use of more risky medicines, such as GlaxoSmithKline's diabetes drug Avandia (rosiglitazone).

Hamburg is using Sharfstein's departure as an opportunity to re-examine the agency's top management structure. Previous commissioners have tried various senior-staff arrangements, with deputy commissioners, chiefs of staff, and special assistants, and Hamburg may move away from the current one-deputy plan.

Counselor to the Commissioner John Taylor is filling Sharfstein's shoes while the commissioner weighs her options, and he is expected to assume a more visible role at the agency in the future. Taylor has had a long career at FDA in legal, enforcement, and regulatory affairs positions under several FDA commissioners during both Democratic and Republican administrations. He rose to be associate commissioner for regulatory affairs from 2002 to 2005 and then served brief stints at Abbott Laboratories and with the Biotechnology Industry Organization. Taylor returned to FDA in 2009 to be Hamburg's top legal advisor, and the commissioner might well prefer to have such a seasoned enforcement official represent FDA before Congressional committees probing enforcement and safety issues.

**Hamburg is using Sharfstein's departure as an opportunity to re-examine the agency's top management structure.**

### More transparency

One of Sharfstein's last activities at FDA was to unveil the third phase of the agency's transparency initiative, a program he headed as chair of the agency's Transparency Task Force. Launched in June 2009, the initiative first created an FDA Basics webpage that presents general information on agency operations and public health policies. Next came an FDA-TRACK program to provide the public with measures of the performance and accomplishments of agency offices and regulatory activities.

This latest segment of the project aims to provide regulated companies with useful information on FDA policies and procedures. Some of this will be on the agency's newly launched FDA Industry Basics webpage. In addition, FDA intends to post more information on key staffers and meeting presentations, provide a system to answer industry questions quickly, and clarify agency review processes as well as its system for developing new guidances and regulations. FDA also seeks comments on several draft proposals that are more complex and difficult, such as whether to set specific timelines for guidance development and how to handle sponsor requests to appeal agency decisions.

More significant for industry is FDA's rejection of two other transparency initiative proposals. The agency decided it will not issue binding advisory opinions on the legality of certain marketing and information practices by companies, as sought by industry, similar to practices of the HHS inspector general and the Federal Trade Commission. FDA says that, instead, it will continue to provide advice on whether promotional pieces for drugs meet regulatory standards prior to dissemination, but retain the right to change its opinion later on. Issuing binding advisory opinions "may place inappropriate restrictions on FDA's ability to respond to emerging issues to best protect and promote the public health," the agency stated in its January 2011 report, "Improving Transparency to Regulated Industry."

FDA also will not commit to notifying companies before publicly disclosing information about the safety of a regulated product. The agency will try to discuss emerging quality problems with the manufacturer, and the Center for Drug Evaluation and Research (CDER) will aim to notify sponsors at least 24 hours in advance of plans to post drug-safety information. However, FDA may post information about a safety issue before consulting with the manufacturer if it feels it is necessary to do so to protect public health.

Sharfstein is leaving FDA without resolving the most contentious disclosure proposals issued in its phase-two transparency report, which was issued in May 2010 (see *Pharmaceutical Tech-*

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*nology's* July 2010 Washington Report column). Specifically, the transparency task force continues to evaluate dozens of comments on whether FDA should make public a broad range of confidential regulatory information, such as when a manufacturer files an investigational application and whether such an application is put on hold, withdrawn, or terminated. A key issue is whether to disclose when a company submits a market application for a new drug, biologic, generic drug or medical device, or when that application is withdrawn or abandoned by the sponsor at a later date. Also in question is whether the agency should make public refuse-to-file or complete response letters. FDA is considering expanded disclosure of information from adverse-event reports, evaluations of imports, plant inspection reports, and product recalls as well.

These issues raise "very interesting legal issues" as well as additional resource requirements, Sharfstein explained at his last FDA media briefing. Agency teams are assessing multiple comments on these proposals, and the review is "on track," but resolution is not expected anytime soon.

## Fighting fakes

In his position as a key advisor to Commissioner Hamburg, John Taylor heads FDA's emergency, counterterrorism, and crisis-management activities, which involves him in efforts to combat drug counterfeiting and adulteration. In December 2010, Taylor represented the agency at a White House forum on intellectual-property (IP) theft organized by the Office of Intellectual Property Enforcement in the Office of Management and Budget. Attorney General Eric Holder headed a list of top administration officials voicing concern that IP theft has serious economic consequences for firms seeking to market legitimate goods, while also threatening the health and safety of consumers. Holder highlighted Justice Department efforts to step up enforcement of pharmaceutical IP cases, such as the successful prosecution of sellers of fake cancer medications and a conviction in Houston, Texas, for selling counterfeit drugs manufactured in China that contained a substance used to manufacture sheet rock.

Fake medicines appear to be a growing problem. At the White House forum, Tom Kubic, president of the Pharmaceutical Security Institute (PSI), reported on data documenting a 700% increase in counterfeit-drug incidence worldwide from 2002 to 2009. Halting the sale of counterfeit drugs is particularly difficult because it's relatively easy to make these products, explained John Clark, vice-president of global security at Pfizer during the forum. All it takes is a large garage, an air compressor, and some kind of blender, Clark noted. It's more difficult to obtain a good tablet press, he added, but fraudulent operators manage to do that as well.

One strategy for combating distribution of knock-off medicines is to crack down on unregulated online pharmacy websites. The Alliance for Safe Online Pharmacies is tackling this problem, as is a new nonprofit organization targeting illegal Internet pharmacies. The coalition is supported by leading Internet commerce companies, such as Google, Microsoft, Yahoo!, MasterCard, Visa, and American Express, and will establish and maintain a registry of legitimate online pharmacies as one way to distinguish them from unethical operators.

One aim of the White House meeting was to build support in the business community for an Anti-Counterfeiting Trade Agreement (ACTA) that is being negotiated with the European Union, Japan, Canada, Switzerland, and other industrialized nations. Even though counterfeit drugs are a growing problem at home, the US situation pales in comparison to the spread of fake medicines in developing nations. As much as 25% of the global drug market may be counterfeit, according to the World Health Organization, and sales of phony medicines add up to some $75 billion per year. Despite objections that the pact might stymie access to lower-cost generic drugs and biosimilars, a final agreement is expected this year.

A primary challenge in blocking counterfeit drugs is to convince the public that knock-off products that appear similar to genuine drugs may be unsafe or ineffective. "Many consumers don't take this as a serious threat to public health," observed Carmen Catizone, president of the National Association of Boards of Pharmacies. No one will take action until "they see dead bodies," he said.

This situation, however, may change as evidence emerges of more fatalities linked to counterfeit drugs. Widely prevalent counterfeit malaria treatments have been implicated in the deaths of thousands of people abroad. Taylor cited a rise in seizures among epilepsy patients, which turned out were related to a counterfeit active ingredient in a widely used treatment. "We see our job as preventing death and harm," Taylor explained during the White House forum. Yet, he noted that alerting the public to the dangers of counterfeit medicines raises the prospect that some patients may get nervous and stop legitimate treatment.

To ensure the safety of imports and drug-supply lines, FDA is developing a risk-ranking system for imported active pharmaceutical ingredients to target more risky products for additional sampling and testing at borders. The agency also is establishing standards for track-and-trace systems that can distinguish genuine from counterfeit products. An internal Counterfeit Working Group is coordinating anticounterfeiting efforts across the agency, while CDER has established a Drug Integrity and Security Program in its Office of Compliance to focus on counterfeiting, diversion, cargo theft, and other supply-chain threats.

FDA may enhance its oversight of global drug manufacturing further through its new membership in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (see page 83 for full story). The decision to admit FDA to the coalition, which became effective last month, comes just in time for Commissioner Hamburg to deliver a keynote address to a symposium in Geneva next May celebrating PIC/S's 40th anniversary. **PT**

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**Albert S. Lee and Mark A. Mynhier**

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## Deep process characterization and "lab-on-a-chip" enable SMART bioprocess design.

With thousands of biotechnology companies worldwide, development of biopharmaceutical therapeutics is highly competitive. Revenue, market share, and earnings from sales of ethical biopharmaceutical drugs are crucial financial drivers today, but a robust research and development (R&D) pipeline assures success and longevity. To succeed in the long term, innovator companies must develop and launch new drugs consistently. Most "low-hanging fruit" research targets have been developed, leaving research teams to rely on more innovative discovery and development capabilities to identify novel targets that not only address unmet medical needs, but also demonstrate potential for fulfilling top-line growth objectives. Similarly, follow-on biologics companies must expedite development of biosimilars of existing blockbuster drugs prior to patent expiration or risk losing market share to generic-drug competitors. When a promising drug candidate is identified, a high-performing organization will develop a SMART biomanufacturing process rapidly to address unmet medical needs and achieve performance targets. SMART processes are: **S**calable to commercial manufacturing scale, **M**odeled based on comprehensive and exhaustive data sets, **A**daptive to meet acceptance criteria at operating limit thresholds, **R**ational to justify established process parameters based on performance data, and **T**ested to assure confidence in process robustness and reproducibility.

Similar to the fields of bioinformatics and genetics in the 1980s, wherein scientists analyzed and mined whole genomes to identify disease-causing therapeutic targets, there is a wealth of historical bioprocess development data in the field of bioprocess engineering. These data can be analyzed and mined to identify SMART bioprocesses for major classes of drugs (e.g., full-length monoclonal antibodies). Best-in-class companies will access their development documentation and data to develop platform processes, requiring only platform process confirmation studies to prepare them for use on novel or biosimilar drug candidates. For more complex drug candidates, these organizations will employ quality-by-design (QbD) principles coupled with multivariate design of experiment (DOE) studies to increase process understanding and enhance predictive capabilities. Ultimately, deep process characterization will enable them to employ SMART bioprocess design principles to increase the speed and likelihood of success of developing clinical and commercial manufacturing processes.

To fully realize the potential of SMART bioprocess design, data, data, and more data are required to drive correlation of the physicochemical properties of a biotherapeutic protein (e.g., primary amino acid sequence, tertiary structure, surface charge distribution, surface hydrophobicity/hydrophilicity, aggregation state, glycosylation patterns) and their effect on fermentation, recovery, formulation, and analytical bioprocess parameters. The challenge is how to execute studies to generate a high volume data for analysis. Multivariate DOE studies are inherently elaborate and require significant data and time for analysis. Even a simple full-factorial DOE study investigating only five factors (e.g., pH, salt, concentrations, buffer, time) of two levels each (e.g., low and high), requires a minimum of $2^5$=32 experiments and the associated full-time equivalents (FTEs) and materials to complete. Material availability is also an issue, especially early in development when expression titers and yields are generally low, with laboratory- and pilot-scale studies generally performed on liter and hundreds-of-liter scale, respectively.

To overcome these challenges, high-throughput, automated, scale-down systems that accurately mimic at-scale bioprocess behavior can be implemented to expedite study execution that requires minimal FTEs and materials, yet generate a high volume of data. Lab-on-a-chip approaches represent the ultimate scale-down mode for bioprocess development that, if realized, can shrink bioprocess development to the sub-microliter scale. Not only can automated methods be used to execute studies, but also they can be invaluable for sample testing and data collection for the orders of magnitude increase in data output. In this laboratory of the future, fermentation, recovery, and formulation parameters can be developed using SMART bioprocess design to maximize expression titers, recovery yields, and shelf-life stability, respectively. The wealth of data that is generated can serve as a repository for data-mining to develop robust manufacturing processes in silico, based simply on amino-acid sequence and protein structure.

Novel approaches and technologies are needed to meet the evolving challenges of biopharmaceutical R&D to identify blockbuster therapies and develop the bioprocesses required to economically manufacture drugs that consistently meet product quality expectations. SMART design principles enable companies to meet those challenges ahead of competitors and facilitate bottom- and top-line growth targets. **PT**

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# Preventing Temperature Abuse

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**Hallie Forcinio**

## Innovations protect the quality of temperature-sensitive products from the plant to the patient.

It's hard to predict exactly what conditions a drug will experience during the distribution process. Will delivery be delayed for a day or more by a blizzard, flood, hurricane, power outage, or holiday weekend? Will the product sit in the sun for hours before it's loaded onto a plane or clears customs?

As air-cargo screening rules tighten, shippers fear that the frequency and length of delays will increase. Delays can be disastrous for temperature-sensitive drugs. If temperature abuse renders a drug ineffective or hazardous, it poses a danger to patients. Monetary losses can be significant, too. Because many temperature-sensitive drugs carry extremely high price tags, a single temperature-abused shipment can cost millions.

To protect products from temperature abuse, drugmakers rely on an expanding array of tools to maintain shipments at the proper conditions. These tools also identify excursions above or below the required temperature range.

The latest temperature-protecting packaging also qualifies as sustainable. Today's designs tend to weigh less and occupy a smaller footprint than previous containers. In addition, they are less likely to rely on dry ice. Thermal containers frequently are both reusable and recyclable, and may contain recycled content, too. Formalized reverse-logistics programs simplify container reuse, cut costs, automate replenishment, and ensure that recyclable components are reprocessed rather than consigned to landfills when they can no longer be reused.

A prepaid shipping label expedites the return of the containers. Upon receipt, all containers are visually inspected, and any damaged components are replaced. Next, the containers are cleaned in compliance with 21 *CFR* 211.94. Before returning to service, thermal components are tracked by customer and serial number and tested to confirm that thermal performance has not degraded (AcuTemp Reusable Enviro-friendly Program Assuring Quality for AcuTemp Qualified Shippers, AcuTemp Thermal Systems).

Another program that inspects, refurbishes, cleans, and sterilizes returned containers is supported by web-based software. The software provides continuously updated reports and alerts on container status, inventory levels, and maintenance needs and allows a user to track its shipments (Credo Encore reverse-logistics services, Minnesota Thermal Science, MTS).

### Temperature control

To protect temperature-sensitive shipments better, several carriers have established specialized service programs and adopted standardized temperature-control technology (Temp Control service, United Cargo, and AC Cool Chain, Air Canada Cargo).

For air transport, this specialized service may include buying or leasing active temperature-controlled containers with proprietary air-movement, heating, cooling, and insulation systems that eliminate the need for dry ice. The compressor-equipped units, which are approved by the Federal Aviation Administration, the European Aviation Safety Agency (EASA), and Transport Canada, operate for more than 100 h on battery power, maintain temperatures between 4 and 25 °C in ambient conditions ranging from −30 to 49 °C, and provide payload space large enough to hold a full pallet. Longer hold times are possible if the unit can be plugged into an AC power outlet. The containers have successfully undergone operational qualification (OQ) at several pharmaceutical companies, including Pfizer. The OQ involved testing under a wide range of temperature setpoints, ambient conditions, shipping lanes, payload sizes, and transit durations (AcuTemp RKN Temperature Management Cargo Unit, CSafe).

A large, compressor-based heating–cooling unit capable of maintaining a

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**Hallie Forcinio** is *Pharmaceutical Technology*'s Packaging Forum editor, 4708 Morningside Drive, Cleveland, OH 44109, tel. 216.351.5824, fax 216.351.5684, editorhal@cs.com.

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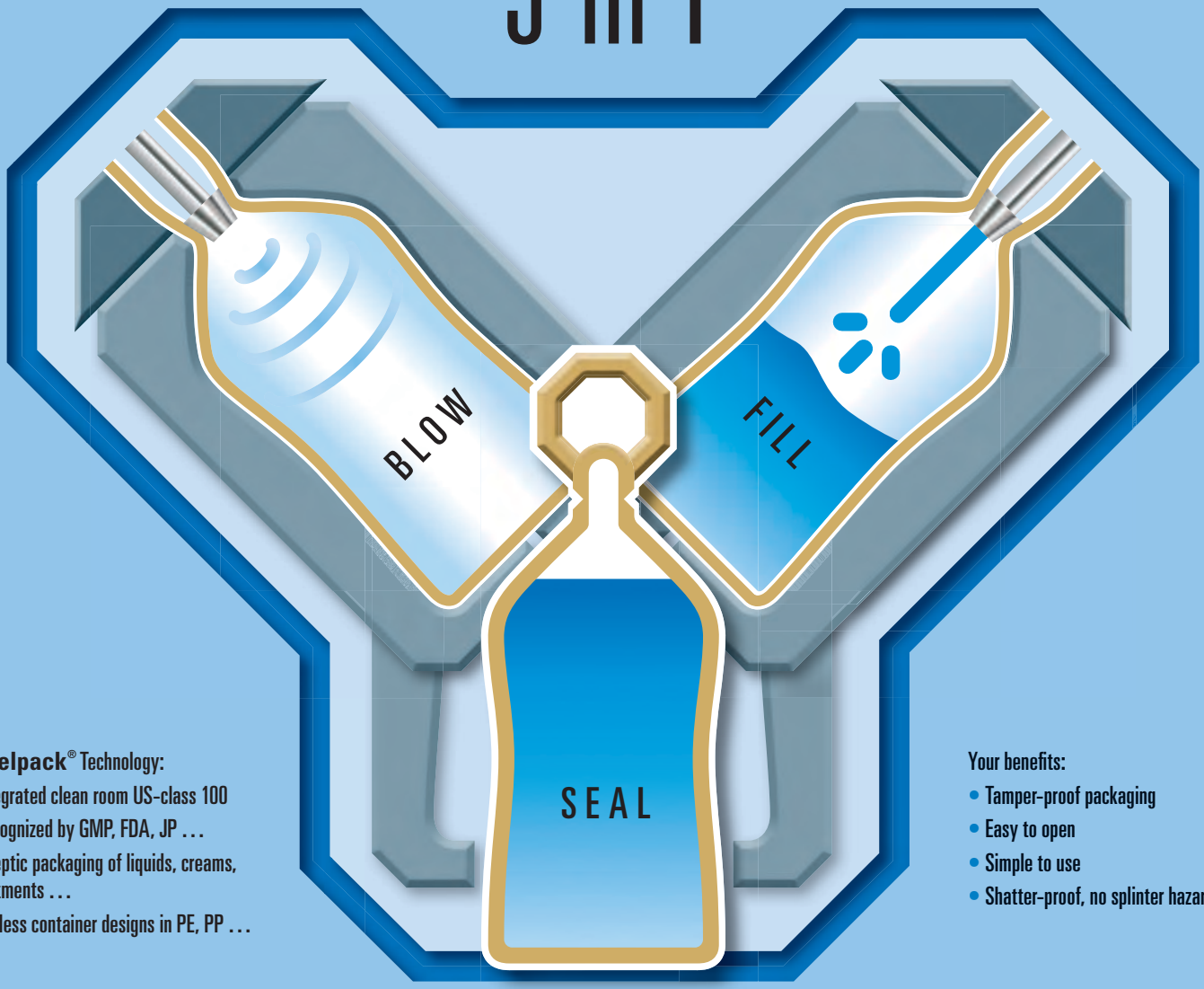


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temperature-controlled environment for five European-sized or four US-sized pallets recently received an airworthiness certification from EASA. It maintains internal temperature between 0 and 25 °C in ambient conditions ranging from −25 to 50 °C (RAP e2 container, Envirotainer).

A passive pallet-shipper system for full or half pallets provides thermal protection for more than 120 h (i.e., five days) without requiring any power. The design relies on phase-change material and vacuum-insulated panels. The reusable system provides a 48 × 40 × 52-in. space with a payload capacity of 890 L (31.4 $ft^3$) or a 48 × 40 × 30-in. area that holds 406 L (14.3 $ft^3$) (Credo Xtreme pallet shipper, MTS). The pallet shipper is part of a range of reusable thermal containers (Credo Cube) that are used by the largest temperature-controlled healthcare transportation provider in Canada (ATS Healthcare).

Another passive system consists of a lockable trunklike unit that is durable, reusable, and compatible with security scanning. Capable of maintaining temperatures between 2 and 8 °C for as long as five days, the system is available with payloads of 36 L (1.27 $ft^3$) and 11 L (0.4 $ft^3$). An optional data logger records downloadable internal and external temperature data to show whether the internal temperature remained in spec throughout the shipment's travels (Kodiak Active Temperature Control Shipping Containers, Active CC Boxes).

A similar reusable design with handles and a latch relies on plant-based phase-change technology and encapsulated vacuum-insulated panels to boost performance while reducing weight. The passive temperature-controlled system produces about seven times the insulating effects of common alternatives such as expanded polystyrene and polyurethane (OrcaTherm temperature-controlled packaging, Intelsius).

For less stringent applications, a passive system maintains an 11 × 11 × 5.5-in. (0.4 $ft^3$) payload area in the 2–8 °C range for 72 h. It consists of gel packs, expanded polystyrene (EPS) panels, and an outer plastic or corrugated case. The unit holds 1 to 7.5 lb of product (TimeSaver 72, Cryopak). All components of the packaging are recyclable, and the EPS insulating panels contain as much as 20% postindustrial recycled content.

Another advantage of the design, which won a Greener Package Award in 2010 from Summit Publishing, is the energy- and time-saving nature of the phase-change material used as the core refrigerant. It freezes and thaws at 5 °C and does not need to be pre-conditioned in a refrigerator or freezer (Engineered Phase 5 phase-change material, Cryopak).

For smaller quantities that are delivered quickly, an inflatable thermal envelope maintains the contents between 2 and 8 °C for as long as 24 hours. Patented construction blocks heat transfer and cushions the product, too. Delivered inflated, the reusable pouch features a zipper closure and dual compartments: one for product, and one for cooling-gel packs. It's available in 1-, 3-, and 5-L sizes (One Day pharmaceutical pouch, Coldpack).

## Temperature monitoring

Data loggers provide a warning if the contents of an insulated package or container experienced heat or cold beyond acceptable parameters. The devices permit immediate decisions about product quality. The ability to upload temperature data from the monitor as soon as the shipment arrives eliminates delays and quarantine time associated with waiting for a monitor to be returned for analysis or a report to be faxed (Shipping Temperature Electronic Monitoring System, Almac Clinical Services).

A specialty courier service tracks the temperature and movement of sensitive shipments in real time through a customized global positioning system (GPS)-based device. It also can provide chain-of-custody data (GPS Tracking devices, GTX, for MNX).

Integrating a satellite network with tracking software achieves similar functionality. The two-way communication between shipping container and shipper or recipient enables real-time product tracking and management and provides an early warning if temperatures deviate beyond desired parameters (SmartLink Platform, Axeda, and satellite network, ORBCOMM).

Yet another way to track temperatures


**AcuTemp RKN Temperature Management Cargo Units for air transport of temperature-sensitive goods.**

inside shipping containers relies on an active radio-frequency identification (RFID) tag equipped with a satellite modem and GPS receiver. If an RFID reader is within range, the tag communicates with it. If not, it uses the satellite modem to upload environmental data and location coordinates (GlobalTag ST-694 and SmartChain software, Savi Networks).

Another RFID-based data logger also relies on an RFID tag–temperature sensor combination. The semipassive tag is compatible with most Gen2 ultrahigh-frequency RFID readers and features a thin profile, easy-to-use manual interface, and 16 configurable temperature ranges between −20 and 70 °C. As many as 4000 data points can be collected. Algorithms calculate the product's remaining shelf life to provide data to support a decision to deliver or return a product that has experienced temperature abuse. Deutsche Post DHL has adopted the technology for its Smart Sensor Temperature service for temperature-controlled shipments (RT0005 easy2log Temperature Logger, CAEN RFID).

RFID technology also is the basis for a label that records temperature information. At any point during the distribution process, a wireless reader can collect data from 30 labels located within 60 ft (20 m). Reading distances as great as 300 ft (100 meters) are possible if the line of sight between reader and label is unobstructed. Available in both the United States and Europe, the flat labels are about the size of a credit card (Ultra Wireless Label and Ultra Wireless Reader, PakSense).

Similar capabilities are provided by high-frequency 13.56-MHz RFID tags and

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The International Air Transport Association's time- and temperature-sensitive label.

PHOTO IS COURTESY OF THE INTERNATIONAL AIR TRANSPORT ASSOCIATION

readers designed for humid environments (SensTag sensor, Phase VI Engineering, based on the MLX90129 sensor IC, Melexis Microelectronic Integration Systems; 13.56-MHz reader from Proxima RF).

A temperature-control process, designed especially for clinical-trial shipments, consists of an RFID tag for recording temperature, a dedicated compartment for a mobile phone for high-speed data transmission, and a secure web-based portal. Designed to record temperatures between 5 and 35 °C at configurable intervals, the device can track more than 8000 data points and operate for nearly 60 days. If the data show that the temperature remained within specifications during shipment, the drug can be released immediately for use (RFID tag, Stora Enso; multimodal communication, MediXine Oy; Clinical Logistics Services, Parexel International).

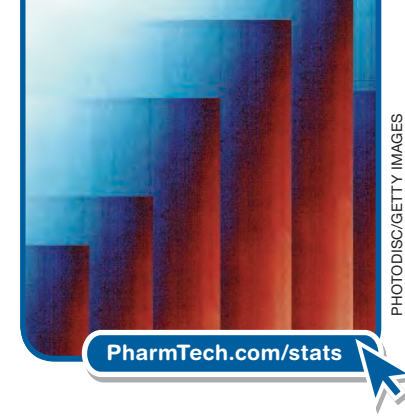
## Standards

Several groups, including the Parenteral Drug Association, the International Safe Transit Association (ISTA), International Air Transport Association, and the US Pharmacopeia are working on tools, guidelines and regulations to support Good Distribution Practices. ISTA recently released its *Standard 20: Design and Qualification of Insulated Shipping Containers*. It includes multiple appendices and worksheets to support the design, testing, and validation of insulated shipping containers. ISTA's new *Standard 7E: Thermal Transport Packaging Used in Parcel Delivery Systems* updates *Standard 7D.*

With the development of Standard 20 and Standard 7E A, ISTA also established new certification categories. A handful of laboratories have completed or are working to be designated as ISTA Certified Thermal Transport Laboratories, and personnel have begun the process to earn Level I or Level II status as ISTA Certified Thermal Professionals. Laboratory certification must be renewed every two years.

Thermal packaging, developed and tested according to the ISTA standards, is designed to simplify the sourcing process and provide confidence in its performance. "Drugmakers will be able to buy ISTA-certified thermal packaging off the shelf with all the necessary documentation and validation information," predicts Ed Church, president of ISTA. **PT**

WEB For a list of guidelines for maintaining the cold chain, visit PharmTech.com.

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# The Promise and Threat of Quality Risk Management

**Jason J. Orloff**

## Using risk assessment properly can provide industry with a unique tool for quality control.

As a tool for the appropriate prioritization of resources, quality risk management (QRM) holds great promise for patients, government, and industry. Just as great, however, is the potential for QRM to degenerate into a non-value added exercise of identifying noncritical, improbable, low-risk scenarios indefinitely. The key to which way it goes is understanding a typical distribution of uncontrolled systems, that is, the Pareto Plot.

As a statistician, I have never been comfortable with subjective risk analysis. The process is fundamentally imperfect because it cannot anticipate the unknown. Furthermore, it lacks the rigor of actuarial risk analysis, which is beyond all but the most critical factors related to safety and efficacy. After conducting tremendous research and development to turn data into process knowledge, it seemed a disappointing end to boil all the information down to a human judgment call. Translating that effort into a subjective scale of 1 to 10 for severity, probability, and detectability left me wanting more than a notional approximation. However, after three days of discussion with the authors of the International Conference on Harmonization's quality guidelines, Q8, Q9, and Q10, at an ICH workshop in Washington, DC, last fall[1] I've gained a new understanding of risk assessment's value.

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Risk assessment enables subject-matter experts to say to the best of their ability, "This is important, and that is not." Risk assessment is not a perfect tool by which analysts can anticipate all dangers—known and unknown—but it is valuable precisely because we cannot anticipate all danger. Risk assessment provides a framework within which to capture the knowledge upon which we have made risk-control decisions. Within this framework, learning can be fed back for capture and future review. The QRM process then enables management to establish priorities and move a project forward from the laboratory to manufacture with an understanding of, diligent control of, and conscious acceptance of risk.

Because risk assessment and control fundamentally rely on hypothesis, judgment, and expert opinion, it is open to endless attack and argument. The resolution of which must be the test of reason. The goal is to draw a line between the "vital few and trivial many" scenarios. This pattern was first recognized by Dr. Joseph M. Juran in 1951 when he coined the Pareto Concept of Quality, giving us a powerful conceptual and visual tool.

As an hypothetical example, Figure 1 shows a Pareto Plot of process parameters for the Sakura Tablet case study, which was last revised in March 2009 by the Japan National Institutes of Health. The figure illustrates the Pareto concept also known as the 80/20 rule. Many factors in a system are trivial and only a few factors are vital. As a rule of thumb, about 80% of the problems come from roughly 20% of the factors identified. The plot provides insight into several aspects of risk management.

First, it can be seen that the factors have been ranked by the magnitude of their risk. As one moves away from the origin, the effect of subsequent factors decays logarithmically. Some factors clearly cause more risk. "The level of effort... should be commensurate with the level of risk," according to the ICH Q9 guideline. These vital factors require the greater investment of resources.

The second point is that, following a logarithmic distribution, the identification of low risk, noncritical, and improbable factors extends infinitely while their risk approaches zero. But where do we draw the line between the vital few and the trivial many? Ultimately, that is a judgment call for negotiation between industry and regulatory authority. However it is a judgment call to be made by experts backed with an in-depth understanding of the underlying science and a common covenant to work on what is vital. The Pareto Plot does not provide hard lines of priority but can allow the negotiators to see the magnitude between what is vital, what is perhaps important, and what is neither.

Risk analysis provides a starting point for continual improvement. It is the best tool we have today for recogniz-

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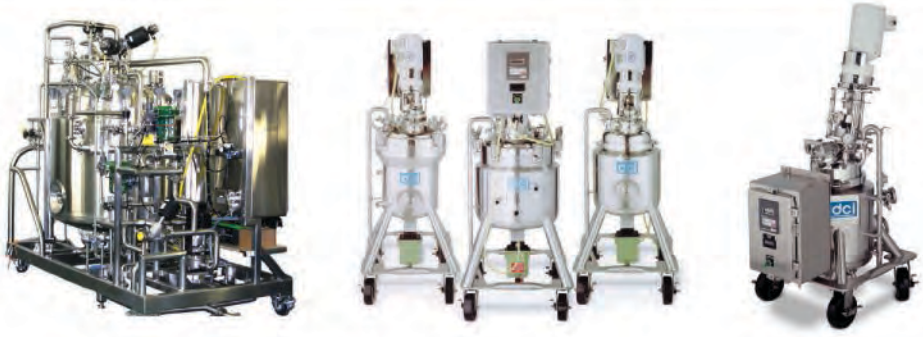

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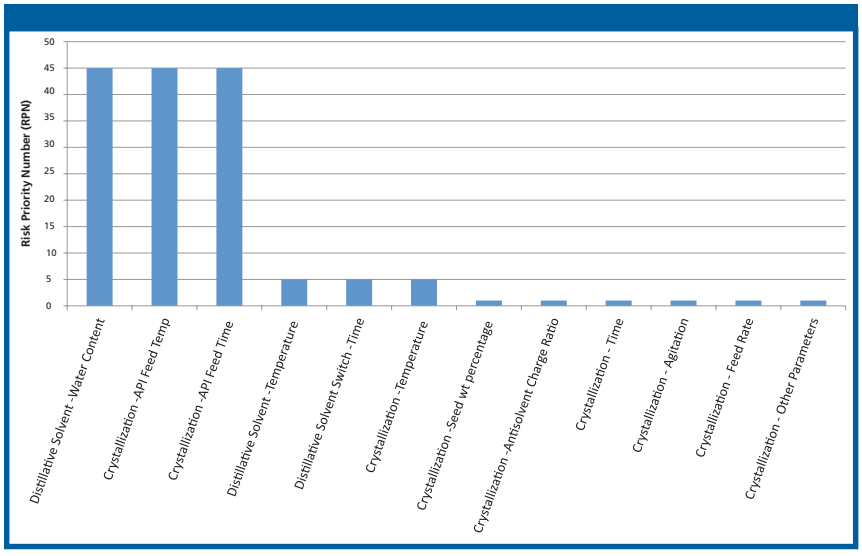


**Figure 1:** The Pareto Plot of Risk Priority Number (RPN), where risk=severity * probability * detectability. The RPN informs the control strategy. As a process improves the probability or detectability changes, and the RPN adjusts accordingly.

ing our imperfect understanding, prioritizing the work before us, and committing ourselves to the iterative process of improvement. In the pre-Q8, Q9, and Q10 world, the inability to admit that our understanding was incomplete and that our systems were imperfect meant a tremendous investment in maintaining a perception to the contrary and generated a culture of mutual distrust. If applied correctly, the post-Q10 world could enable industry to move beyond a philosophy where every batch of a product is expected to be a replicate of the validation runs.

Instead, we should set out with the intention to change our processes. We should be able to change them for the better. The key is to recognize risk assessment as an ongoing process that combines both objective science and subjective judgment to appropriately prioritize the allocation of resources. As the risk-control strategy is refined, risk is reduced, and new priorities emerge. Our effort must be applied to the vital few things that matter. **PT**

*Note: The ideas in this article were generated during the October 2010 "Integrated Implementation Training Workshops for ICH Q8, Q9 & Q10," which took place in Bethesda, MD.

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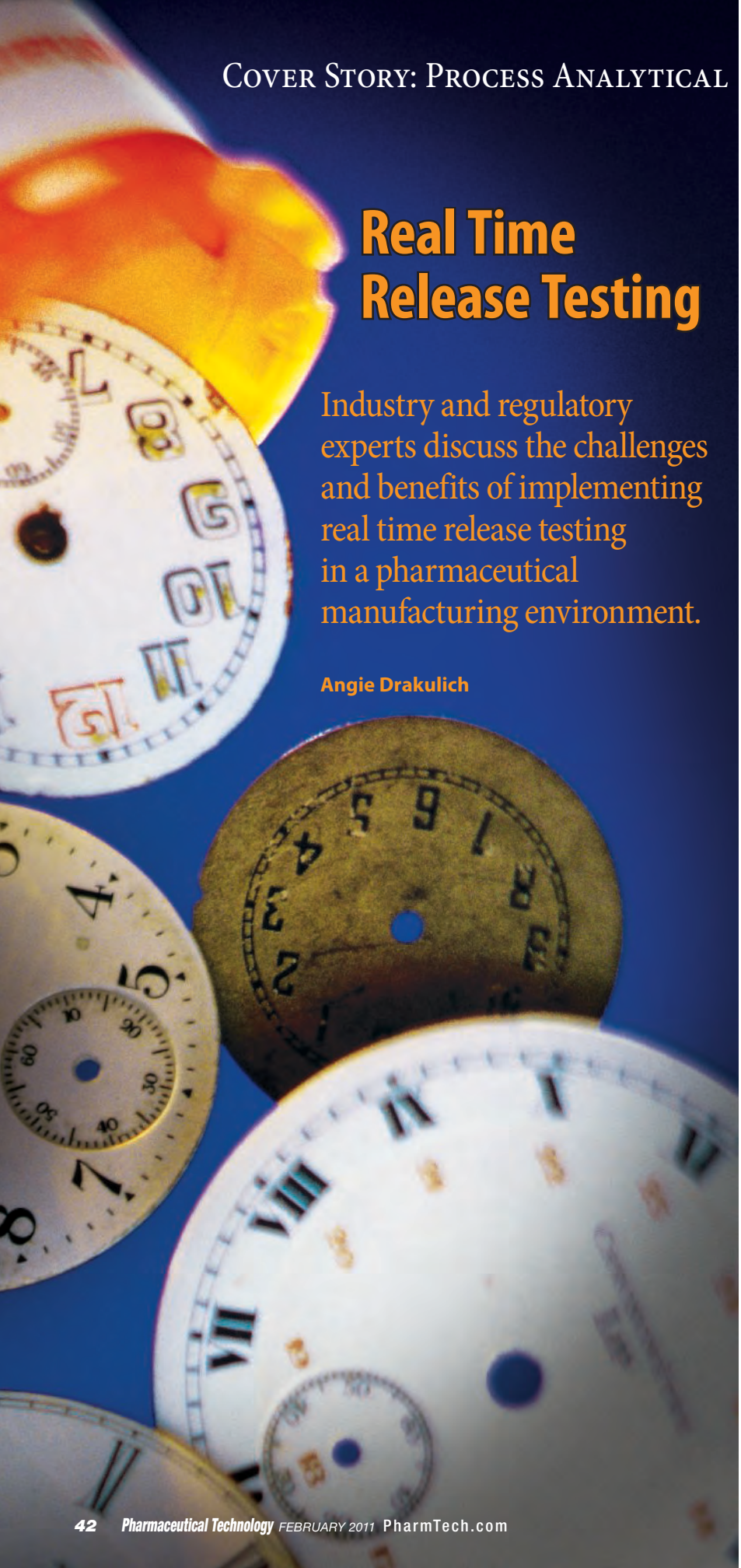

# Real Time Release Testing

## Industry and regulatory experts discuss the challenges and benefits of implementing real time release testing in a pharmaceutical manufacturing environment.

**Angie Drakulich**

In 2004, FDA published a final guidance for industry introducing the concept of process analytical technology (PAT) and redefining pharmaceutical manufacturing and quality assurance for the future. That guidance also addressed a concept known as "real time release," defined as "the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data" (1). The PAT component includes, according to the guidance, "a valid combination of assessed material attributes and process controls," and builds upon the 1985 guidance on parametric release, which is used primarily in heat-based sterilization of drugs.

A few years later, in August 2009, the parties to the International Conference on Harmonization (ICH) adopted ICH Q8(R2) *Pharmaceutical Development*, which used the term "real time release testing" (RTRT). The definition of this term in ICH Q8(R2) shifted the emphasis from the decision to release a batch to the measurements themselves, as follows: "the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls."

There are many benefits to be gained from RTRT applications. "From an industry standpoint, RTRT approaches seem to have economic benefits from manufacturing efficiency, such as reduced inventory and lower laboratory costs," says Christine Moore, PhD, deputy director for science and policy at the FDA Office of New Drug Quality Assessment (ONDQA), which falls under the Center for Drug Evaluation and Research (CDER). "Quality can also benefit resulting in higher yields or lower rework or rejection rates. From a regulator's and a consumer's standpoint, the integrated real-time analysis and control feasible with RTRT have the potential to provide an increased assurance of product quality."

Adds Grace McNally, senior policy advisor within FDA's Division of Manufacturing and Product Quality, Office

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of Compliance, which also falls under CDER, "One of the benefits of on-line or at-line testing is the ability to perform rapid analysis in real-time. PAT tools typically enable nondestructive testing and provide the opportunity for enhanced monitoring during the manufacturing process, and greater product and process understanding."

Despite the potential gains that can be realized from RTRT, industry still is trying to work out the practicalities of implementing the approach, and therefore, is not yet fully benefitting from its promises. Many questions remain regarding the instrumentation to use, when and where on the manufacturing line to conduct tests, how to evaluate on- or in-line analyzers during manufacture, and what regulatory authorities expect.

Industry's hesitation toward applying RTRT was abundantly clear during the October 2010 ICH Quality Implementation Working Group (IWG) workshop, held in North Bethesda, Maryland. A breakout session on control strategy addressed RTRT controls and brought up even more questions about its application, such as what to do in case of instrumentation failure, how to differentiate between RTRT and in-process tests, how to describe RTRT in specification, and where to record RTRT information in regulatory submissions, such as the common technical document.

**"*In-situ* measurements allow for true real-time monitoring, which is significantly better than traditional grab sampling." —Stuart Farquharson, Real-Time Analyzers**

The issue stretches across the Atlantic. The European Medicines Agency (EMA) published a new draft guideline on RTRT just last year to replace its former guideline on parametric release (2). The new document is meant to align better with the ICH terminology and to allow for real time release tests beyond that of sterility testing, which is the most common real time release practice.

During the past nearly two years, the ICH Quality IWG has constructed and posted on its website a list of common questions and answers about the organization's quality guidelines (Q8, Q9, and Q10). The current version includes 11 Q&As devoted solely to RTRT (3). As industry moves more toward a

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quality-based approach, some RTRT questions may fall into place. In the meantime, *Pharmaceutical Technology* gathered input from industry and regulatory experts already making headway in this area.

**"We strongly recommend that companies looking to implement RTRT request a meeting with the FDA to discuss their proposal prior to submission." –Christine Moore, FDA**

### Making the move to RTRT

Now that RTRT has moved from a concept to a realistic option for drug products, says Senior Director of Global Manufacturing Services at Pfizer Global Manufacturing Holly Bonsignore, there are many benefits for industry to take advantage of. For example, RTRT can "improve process control by generating more data while the manufacturing process is taking place, as opposed to traditional release testing conducted on small samples after batch manufacture is complete." The availability of RTRT data at the time of batch manufacture can also improve operational efficiency and inventory control by eliminating the time and resources needed to test batches in a laboratory post-manufacture.

There are a few downsides to the approach as well. Because RTRT is not yet globally accepted by regulatory agencies, explains Bonsignore, manufacturers are caught somewhat in the middle of a paradigm manufacturing shift. Some companies need to continue to use traditional batch-release testing for certain markets even if other markets have approved the approach and even if the company is ready to move full speed ahead with RTRT.

Bonsignore's colleague, Steve Hammond, a director and team leader in Pfizer Global Manufacturing's analytical sciences group, notes a more technical limitation with RTRT: testing for impurities and stability. "PAT technology is being developed that may be capable of that category of 'stability indicating' analysis, but at this time, there is a gap," he explains. "The approach at Pfizer is to propose RTRT for products for which we have a history of stability (e.g., active pharmaceutical ingredients that do not degrade due to the manufacturing process)."

Adds Terry Redman, product manager for particle-system characterization at Mettler-Toledo AutoChem, "It is not always feasible or cost-effective to implement direct measurement of all critical process parameters (CPPs) and critical quality attributes (CQAs) with RTRT. In many cases, gaps in measurement technology must be filled with inferred measurements that must be proven statistically reliable," he says. However, that may change in the coming years. New measurement technologies are on the horizon that will improve industry's ability to monitor process control and provide analytical measurements for quality control.

The key, according to many industry experts, is going to be increased product and process knowledge—a fundamental concept of quality by design (QbD) and the harmonized ICH quality guidelines. As Tim Freeman, director of operations at Freeman Technology, points out, "Although RTRT is the future for efficient, safe and competitive pharmaceutical manufacturing, it relies on capturing more information about the materials being processed and the equipment and configuration employed during manufacturing."

FDA's Moore offers a specific example. "By understanding your process and controlling its associated risks through a PAT system, you can monitor and control the process at the most important points," she says. "Some critical quality attributes, such as dissolution, cannot be measured directly by a specific probe. Instead, to utilize a RTRT approach, you need to understand the relation between the desired product attribute and relevant material attributes and process parameters and then monitor and control them accordingly."

### Selecting appropriate unit operations

In terms of gaining knowledge before applying RTRT to a manufacturing process, pharmaceutical firms may need to determine which operations, from blending and compaction to tablet coating, are conducive to its use. The good news, according to Pfizer's Hammond, is that PAT applications are now well developed for most all unit operations. "For most products, nearinfrared (NIR) can handle a high proportion of unit operations, and the emergence of light-induced fluorescence instruments with an order of magnitude greater sensitivity than NIR has taken PAT into low-dose products," he says. In addition, he notes that technologies such as terahertz spectroscopy are emerging for coating monitoring and control, but says that further development is required in this application area.

In terms of tableting and powder processing, Freeman says he has come across several advances in measurement technologies that are driving material and process understanding toward an RTRT approach. "There are now GMP suites for continuous manufacturing of tablets that rely heavily on PAT and that function with real-time, closed-loop feedback on parameters such as size, moisture content and blend uniformity," he says. "For this reason, RTRT has become much more of a reality in the last couple of years. However, there are many material properties that are still not measured routinely at-line or on-line, even though they will influence final product quality."

According to FDA's Moore, "Many of the sensors used for in-process mea-

surements of pharmaceutical technologies have been well established in other similar industries, such as the chemical or food processing industry. Undoubtedly, there is a sensor available that could be used at every unit operation of tablet or other dosage form manufacturing. Monitoring every step does not necessarily add value though." She adds, "The challenge is to perform the right measurement, at the right time, and at the right location. Furthermore, you want the right control systems in place to make appropriate and timely adjustments to the process based on the information collected."

## Managing sampling plans

Another big challenge to using RTRT is how to approach sampling plans, specifically when and where to take a sample, how much of a sample to take, and whether compendial or risk-assessment issues need to be considered. Explains Alon Vaisman, applications manager of pharmaceuticals for Malvern Instruments, "Usually PAT instruments access larger amounts of sample than would be used for lab analysis. On-line instrumentation would typically utilize automated sampling, in contrast to traditional off-line techniques that tend to rely on grab sampling at the end of the process. Sample preparation is usually relatively limited for PAT systems since this is necessary to achieve the measurement rates required for continuous monitoring."

As for where to do sampling on themanufacturing line, Real-Time Analyzers President & CEO Stuart Farquharson suggests that RTRT is not limited to tablet or pill manufacturing, but also encompases drug synthesis. In this case, the best place to monitor synthesis is *in-situ*, or inside the reactor. This allows monitoring and ultimately controlling the reaction rate, reaction end-point, and yield. "This can be accomplished using a long rod fiber-optic probe. However, efforts must be made to keep the probe head clean. *In-situ* measurements allow for true real-time monitoring, which is significantly better than traditional grab sampling, primarily used to determine when the end point had been reached," he explains.

According to FDA's McNally, "Manufacturers must determine appropriate sampling for their processes. It is important to remember that compendial tests are standards that any compendial drug must meet if tested. Applicants should consider the claims and disclaimers made by each compendium they reference.

"The current *US Pharmacopeia* (*USP* 33–*NF* 28 Reissue), for example, notes that their compendial standards are not intended to make inferences about the larger group of units from which the sample was obtained. The General Notices section also states, 'In all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither

specified nor proscribed by the compendia.' So, manufacturers must ensure sampling sizes and plans are statistically sound and representative of the batch. A quality risk-management approach can be useful to develop an appropriate sampling plan."

Moore adds that the agency is willing to work with applicants to ensure appropriate acceptance criteria for large sample sizes.

Pfizer's Hammond seems to agree that there is work to be done in the area of sampling. "There is the potential to sample very frequently or to take large numbers of units for a measurement," he explains. Pfizer uses a risk-based approach to determine sampling frequency, including looking at how the data is used, what calculations are performed, and what statistics are used for setting a specification.

"There is agreement that conventional statistics do not apply when larger data sets are under consideration. The so-called 'large n' approach is needed. Industry and regulators have been debating the best approach for a while now and some sensible approaches seem to be evolving from this discussion," adds Hammond.

He references a recent PQRI paper published, with FDA input, that describes three possible "large n" approaches. "In terms of sampling of blends during analysis using probe systems, careful control of the amount of sample that contributes to a spectrum is important. Generally the illumination characteristics are engineered to ensure that approximately one unit dose weight of blend contributes to a spectrum. Analysis of tablet cores is generally *via* transmission of light, through the tablet, thus ensuring that most of the material in the tablet core contributes to the spectrum collected."

Overall, the primary purpose of RTRT, and any PAT or QbD application for that matter, is to understand and control one's product and processes in a manner that ensures quality final product.

Sampling needs to be sufficient to facilitate real-time control, generate knowledge to allow the control of the next manufacturing step, and measure critical material attributes. With end-of-line testing, according to one expert, the purpose of sampling is to assess what the quality is, and the testing of samples has two roles: one enables control, and another validates the control system and strategy. Within RTRR, therefore, sampling's role is to assure that the controls are appropriate.

## Dealing with equipment failures

Of great concern among industry is what to do in the event of an equipment or instrumentation failure while an RTRT process or analysis is being run. "Generally, it is not acceptable to discount PAT measurements and return to a conventional approach simply because the PAT fails a batch," says Pfizer's Hammond. "It must be proven that the equipment has malfunctioned in some way. As most PAT instruments now have very sophisticated self-diagnostic procedures, it is better to have the PAT device automatically cease to function if any of the internal diagnostics fail. Thus, suspect results are not generated."

Furthermore, a manufacturer applying an RTRT test that fails might also use a risk-assessment process to decide how to proceed. "The possibility of using the traditional analytical procedures that are registered for the product is something the industry needs to make PAT a viable proposition. All mechanical electrical systems can malfunction, and pharmaceutical manufacturing needs a way to ensure business continuity if a PAT system does break down," says Hammond.

According to FDA's McNally, "In the event of on-line or in-line equipment breakdown, the control strategy provided in the application can include the use of alternative tests or monitoring in case of equipment failure. The alternative approach could involve use of in-process and end product testing or other options, while maintaining an acceptable level of quality."

Of note, EMA's new draft guideline on RTRT includes very similar language with regard to dealing with equipment failure (2). Overall, both regulatory authorities seem to agree that testing or monitoring equipment breakdown needs to "be managed in the context of a deviation under the quality management system and can be covered by GMP" (2).

This may be particularly important for those PAT systems that can produce false negatives, such as those using spectroscopy and chemometric methods, adds McNally. "The manufacturer should ensure an effective calibration pro-

gram is in place. This includes procedures to follow in the case of an out-of-specification (OOS) result from a PAT tool and steps to be taken to maintain and recalibrate the calibration model."

Some of the ICH questions and answers on real time release address this issue in more detail (3).

## Conclusion

To date, the pharmaceutical sector seems to be moving forward with RTRT but at a slow pace. The concept "is no longer treated as an unobtainable goal," says Malvern's Vaisman. "Many companies in industry and in academic research centers are making significant inroads in implementing continuous manufacturing trains and RTRT. That said, RTRT is not yet the norm," he adds.

Cost may be a factor in the rate of implementation, point out GE Analytical Instrumentation's Richard Godec and Jonathan Yourkin, new product development manager, and global pharmaceutical product manager, respectively. Because analytical tools are still being developed and many companies' senior management and quality teams are not yet on board, RTRT is a bit of a double-edged sword. "The main advantage of RTRT is the cost-effective control of the manufacturing process to meet all quality and product specifications. The main disadvantage, however, is that there is an initial investment required to achieve RTRT of finished drug products," they say.

On the regulatory side, FDA "has reviewed and approved several applications using RTRT approaches, but the numbers are still small," says Moore. "The applications containing RTRT approaches have been challenging to review; they not only include new science but also have new approaches to fulfilling regulatory requirements. We (the FDA) are still learning, and every application has different nuances. We strongly recommend that companies looking to implement RTRT request a meeting with the FDA to discuss their proposal prior to submission."

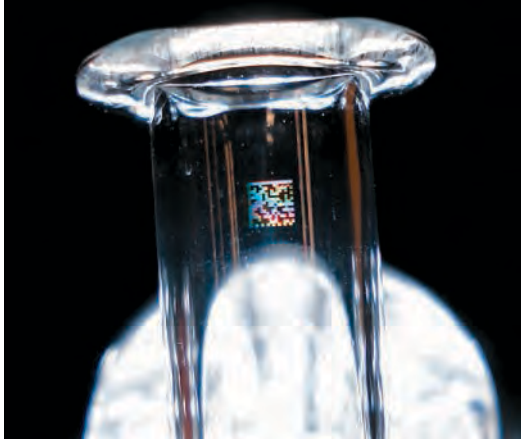
## References


1. FDA, *Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (Rockville, MD, September 2004).
2. EMA, *Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)*, draft, February 2010.
3. ICH, *Quality Implementation Working Group on Q8, Q9, and Q10 Questions and Answers* (Nov. 11, 2010), www.ich.org.
4. FDA, *Draft Guidance for Industry, Process Validation: General Principles and Practices* (Rockville, MD, November 2008). **PT**


**WEB: Read about specific RTRT analytical methods and innovations on PharmTech.com, featuring input from GE Analytical Instruments, Malvern Instruments, Mettler Toledo, and Real-time Analyzers.**

**PLUS, read an overview of RTRT as it applies to powder processing by Tim Freeman, director of operations at Freeman Technology, on PharmTech.com.**

# Securing Pharmaceutical Glass Containers



**Alexis Pellek**

Implementation deadlines for California's ePedigree program are now four years away for pharmaceutical manufacturers. The state's mandatory plan for serialization and traceability of item-level packaging is an important step toward improving supply-chain safety. Manufacturers must begin to roll out serialization starting in 2015, followed by wholesalers and repackagers in subsequent years. Arvindh Balakrishnan and John Danese of Oracle provide guidance in the adjoining sidebar.

A cutting-edge solution for the serialization of glass containers for the pharmaceutical industry uses a laser-coding system that places an identifying mark on individual vials, syringes, or ampoules that does not compromise the stability of the glass. An attractive feature of the system is that it easily integrates into existing production lines. A collaboration between Roche Diagnostics, SCHOTT forma vitrum, SCHOTT-Rohrglas, Seidenader Vision, and Vesdo developed such a solution, which places a 2D barcode containing identifying information, such as batch number or the date and location of manufacture, on a container.

Another coding system for glass containers uses a laser to place logos, alphanumeric text, and 2D barcodes below the surface of the glass, which makes counterfeiting the information extremely difficult. Using a femtosecond laser and proprietary marking technology, TRACKinside's unique identifiers "are made by changing the refractory index inside the glass, which creates a permanent, indelible, and highly readable set of codes," says Adrian Simmons, marketing manager at TRACKinside.

The marks are easy to read, and covert marks that require the use of a scanner for authentication can also be used. The solution is designed for containers made of clear and colored glass as well as clear plastics. The company's laser systems feature marking speeds of up to 10 products per second. TRACKinside's process does not alter the surface of the container or produce microcracks, which would weaken the glass. Because no inks or additives are used, there is no chance of contamination of the product, which means additional FDA approval is not necessary, says Simmons.

TRACKinside's item-level serialization solution provides traceability and authentication capabilities plus added security for pharmaceutical glass containers because the marks are hard to fake. "In addition to product and client information, each 2D barcode can have hidden coded elements therein, as an extra anticounterfeiting feature," Simmons says. He added that "the possibility that counterfeiters can copy this technology is remote." **PT**

## California ePedigree and serialization requirements

California's ePedigree initiative is intended to reduce the incidence of counterfeit drugs within the state's jurisdiction, a move that will have important ripple effects across the nation. It will require manufacturers, distributors, wholesalers, and retailers to provide detailed data to trace products' movement through the supply chain at the unit level—a significant change in an industry that has never tracked beyond the lot level. The California requirements include the following:

- Fifty percent of a manufacturer's products must be serialized by Jan. 1, 2015
- The remaining 50% of a manufacturer's products must be serialized by Jan. 1, 2016
- Wholesalers and repackagers must accept and forward products with the ePedigree by July 1, 2016
- Pharmacy and pharmacy warehouses must accept and pass ePedigrees, sending the information to downstream partners such as wholesalers and repackagers, by July 1, 2017.

Implementation timelines have been postponed several times, leading some manufacturers to step back and delay preparations for compliance. This strategy, however, is shortsighted as ePedigree and serialization will not only help to reduce counterfeiting risk and the associated financial and reputational costs, but can also advance pharmaceutical manufacturers' efforts to improve operational efficiency. For example, more granular inventory visibility afforded by serialization and ePedigree documentation can help to reduce chargebacks, improve returns reconciliation, and, in some cases, allow more targeted recalls.

To prepare, manufacturers should:

- Assess system requirements immediately as information technology is fundamental to ePedigree and serialization initiatives.
- Move forward with radiofrequency identification (RFID) and/or 2D barcodes, which support the realities of ePedigree, including unit-level serialization, item-level tagging, and the capture and management of massive amounts of transactional data.
- Adopt a service-oriented architecture (SOA) approach. To gain the flexibility and agility necessary for an ePedigree initiative, manufacturers require business applications built on an open, standards-based, SOA. An SOA-based mass-serialization and pedigree-management solution provides a scalable and flexible infrastructure for efficient forward and reverse logistics by integrating with a manufacturer's existing back-end transactional systems.

Companies that adapt quickly and embrace ePedigree and serialization will not only be well-positioned for compliance in 2015, but can also count themselves as early benefactors of the business benefits of these initiatives.

*—Arvindh Balakrishnan, vice-president of the Life Sciences Industry Business Unit, and John Danese, director of product strategy, both at Oracle.*

IMAGE COURTESY OF TRACKINSIDE. THE COMPANY'S LASER-MARKING SYSTEM PLACES A 2D BARCODE ON A BD HYPAK SYRINGE.

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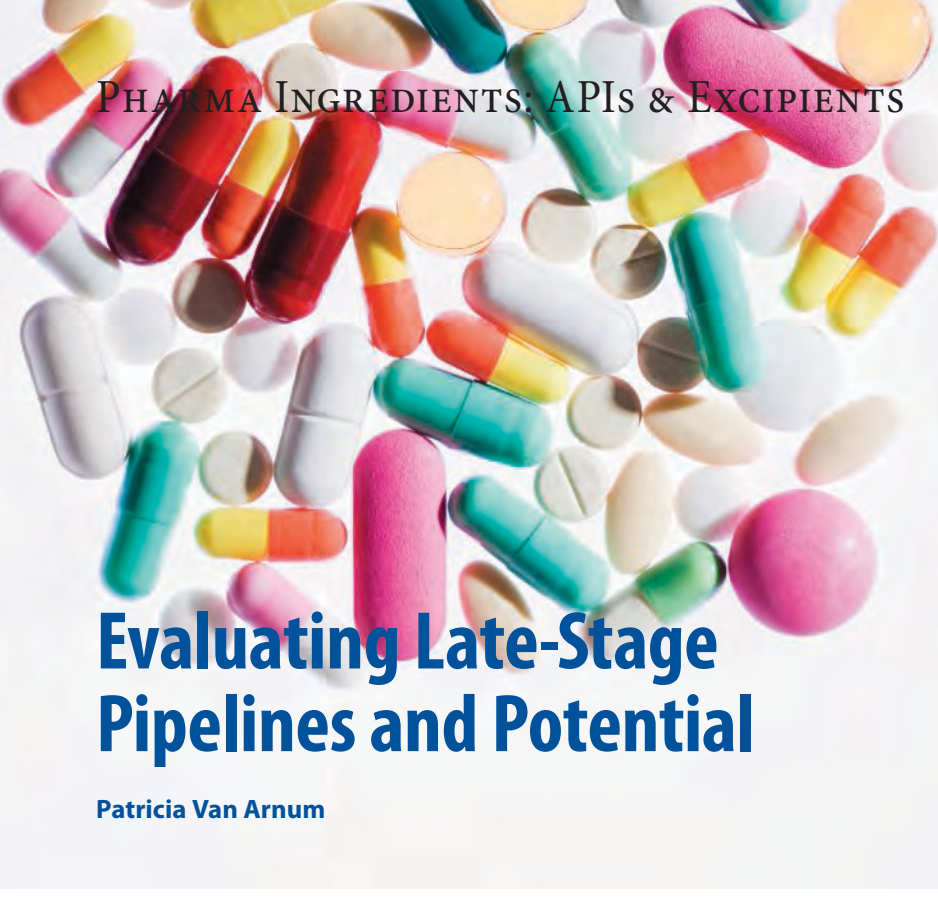


# Evaluating Late-Stage Pipelines and Potential

Patricia Van Arnum

Will 2011 be a more promising year for new molecular entities? A review of Big Pharma's late-stage pipeline shows what might lie ahead.

How robust is the pipeline of the pharmaceutical majors? That is the crucial question not only for the pharmaceutical majors but also for emerging pharmaceuticals that rely on licensing or product acquisition by the large pharmaceutical companies to fund their development efforts.

## The numbers

The well-chronicled problem of a lack of strong recent product innovation, combined with greater incursion of generic drugs, paints a pessimistic outlook for prescription-drug sales by the pharmaceutical majors. A recent analysis by the market-research firm Datamonitor estimates that growth will slow to 1.3% to 2015 for the branded prescription pharmaceutical industry's leading companies. In contrast, between 2003 and 2009, these same companies had sales growth at a compound annual growth rate (CAGR) of 7.1%. Sharp declines in branded sales following the loss of patent exclusivity will drive the decline in growth.

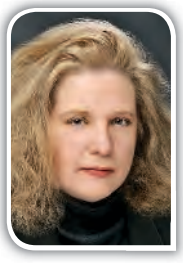
"The difficulty in developing new products, particularly those that can generate sufficient sales to compensate for blockbuster expiries, has compounded this problem," said Simon King, pharmaceutical company analyst at the market research firm Datamonitor, in a Jan. 20, 2011, press release. "This has driven a steady shift away from blockbuster-centric growth strategies toward diversification into other areas of the market." Datamonitor predicts that those companies insulated from generic competition or those able to offset generic-drug incursion from revenue growth sourced from a high biologics focus or the targeting of niche indications and areas of high unmet need will be the best performers."

Datamonitor projects that Bayer, Novartis, Roche, and GlaxoSmithKline will be the only Big Pharma companies generating above average growth through the period to 2015. Of 43 branded companies examined in detail by Datamonitor, 11 are expected to report negative sales CAGR during the period to 2015. Of those expected to deliver positive sales CAGR, only six will exceed the 7.1% average shown between 2003 and 2009.

## Inside the pipelines

**Pfizer.** Pfizer provided an update of its development program, which includes 118 programs from Phase I through registration, as of September 2010. The 118 programs in place was a decline compared with the 133 programs that the company had as of its previous pipeline update in January 2010. The 118 programs reflect 25 drug candidates that are new compounds or other drug that have advanced along the pipeline and 31 programs that were discontinued. The company's pipeline as of its September 2010 update included 26 programs in Phase III development, and nine programs in registration as well as 27 biologics and four vaccines within all phases in development. The company also had 46 projects in Phase I development, and 37 drug candidates in Phase II development.

Pfizer discontinued several late-stage projects when providing an update to its pipeline in September 2010. These withdrawals included several existing drugs that were being developed for additional indications: Sutent (sunitinib) for various oncology indications; Celebrex (celecoxib) for treating gouty arthritis; and Lyrica (pregabalin) for treating restless legs syndrome. The company also discontinued development of a monoclonal antibody in Phase III development, figitumumab, which was being examined for treating non-small-cell lung cancer although the drug continues to be studied for other indications.



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Pfizer has several Phase III oncology drug candidates. Some key candidates include PF-00299804, an investigational, oral, pan-HER (pan-human epidermal growth factor receptor) inhibitor. It is an irreversible small- molecule inhibitor of HER-1 (EGFR- epidermal growth factor receptor)-2 and -4 tyrosine kinase designed to treat lung cancer. Neratinib also is a pan-HER inhibitor and is targeted to treat breast cancer. Bosutinib is an investigational oral dual Src and Abl kinase inhibitor. It is believed that bosutinib may inhibit Src and Abl tyrosine kinases in chronic myeloid leukemia cells that allow the cells to grow, survive, and reproduce. Axitinib is a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor designed to treat renal-cell carcinoma. And crizotinib (PF-02341066) is an anaplastic lymphoma kinase (ALK) inhibitor for treating patients with advanced non-small-cell lung cancer whose tumors are ALK-positive.

Crizotinib was granted fast-track status by FDA in December 2010. In January 2011, Pfizer initiated the rolling submission of a new drug application (NDA) to FDA for crizotinib and expects to complete the submission in the first half of 2011. Pfizer also plans regulatory submissions to FDA and the European Medicines Agency for two other investigational oncology compounds in 2011, axitinib and bosutinib, according to a Jan. 12, 2011, Pfizer press release.

Another important drug to watch from Pfizer's late-stage pipeline is tasocitinib (CP-690550), an investigational Janus kinase (JAK) inhibitor that is being investigated as a targeted immunomodulator and disease-modifying therapy for rheumatoid arthritis. Pfizer reported positive Phase III results in 2010. The company said that the mechanism of action is an improvement compared with the mechanisms of other rheumatoid arthritis therapies that are directed at extracellular targets, such as pro-inflammatory cytokines. Tasocitinib targets the intracellular signaling pathways that operate as hubs in the inflammatory cytokine network. Pfizer also is studying orally administered tasocitinib in psoriasis, inflammatory bowel disease (i.e., Crohn's disease and ulcerative colitis), and organ transplant, and topical tasocitinib in both psoriasis and dry eye.

**sanofi-aventis.** sanofi-aventis had 49 projects in clinical development as of February 2010, of which 17 were either in Phase III, including seven vaccine projects, or pending review for marketing authorization from health authorities. These included nine new molecular entities (NMEs) in Phase III development, and one NME submitted for approval, which was subsequently approved in 2010. Jevtana (cabazitaxel), a novel investigational taxane compound that may be active in cell lines refractory to taxanes, was approved in July 2010 in the US as a second-line use in advanced hormone-refractory prostate cancer in men who have already been treated with docetaxel. The drug was recommended for approval by an EMA advisory committee in January 2011.

Several late-stage NMEs by sanofi-aventis are targeting oncology. These candidates include BSI-201 (iniparib), an investigational targeted therapy, which inhibits poly (ADP-ribose) polymerase (PARP1), an enzyme involved in DNA damage repair. Iniparib is in Phase III trials for treating patients with metastatic triple negative breast cancer (mTNBC) and squamous non-small-cell lung cancer. It also is in Phase II trials for treating patients with ovarian, uterine, and brain cancers. The drug is being developed by sanofi-aventis's subsidiary BiPar Sciences. Iniparib was granted fast-track designation by FDA for mTNBC. The regulatory submissions are planned for the first quarter 2011 in the US and the second quarter 2011 in the European Union, according to a Jan. 5, 2011, BiPhar Sciences press release.

sanofi aventis also is developing aflibercept, a fusion protein specifically designed to bind all forms of vascular endothelial growth factor-A (VEGF-A). VEGF-A is required for the growth of new blood vessels that are needed for tumors to grow and is a regulator of vascular permeability and leakage. In addition, aflibercept binds placental growth factor, which also has been implicated in tumor angiogenesis. sanofi-aventis is developing the drug for several cancer indications with the biopharmaceutical company Regeneron. In January 2011, Regeneron announced that it also started Phase III trials for VEGF Trap-Eye (aflibercept ophthalmic solution) with Bayer Healthcare and the Singapore Eye Research to treat choroidal neovascularisation of the retina as a result of pathologic myopia.

Other late-stage drugs by sanofi include: ombrabulin (AVE8062), which is currently being investigated in Phase III for treating refractory advanced soft tissue sarcoma. Phase III studies also are planned in non-small-cell lung cancer. Another late-stage candidate is alvocidib, a cyclin-dependent kinase (CDK); CDKs are involved in both cell-cycle progression and transcription. sanofi aventis also is partnered with the Danish biopharmaceutical firm Zealand Pharma for lixisenatide, a glucagon-like peptide-1 (GLP-1) drug to treat diabetes. sanofi also is developing otamixaban, an anti-Xa intravenous anticoagulant.

**Novartis**. Novartis reported in November 2010 that it has 142 pipeline projects in pharmaceuticals at various stages of clinical development, of which more than 35% are in Phase III or registration. The company plans to submit 30 regulatory submissions in pharmaceuticals before the end of 2012, inclusive of NMEs as well as additional indications for existing drugs or new formulations.

Novartis was targeting to complete eight regulatory submissions in 2010. These candidates included: a single-pill combination for Tekturna (aliskiren) and amlodipine for treating hypertension; Lucentis (ranibizumab) for treating visual impairment due to macular edema secondary to retinal vein occlusion; Afinitor (everolimus) for treating subependymal giant-cell astrocytoma associated with tuberous sclerosis; and SOM230, an investigational compound to treat Cushing's disease. In 2011, No-

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vartis expects to complete a further 13 regulatory submissions with an additional nine planned for 2012, according to a Nov. 17, 2010, Novartis press release.

Novartis experienced a setback in its pipeline when it decided in October 2010 to discontinue development of two compounds: albinterferon alfa-2b, a drug being developed with Human Genome Sciences to treat chronic hepatitis C, and Mycograb (efungumab), an antifungal agent. The company took an impairment charge of $590 million in the third quarter 2010 for discontinuing these programs, $230 million for stopping development of albinterferon alfa-2 and $360 million for stopping development of efungumab.

**GlaxoSmithKline (GSK)**. GSK has approximately 30 drug candidates in late-stage development, according to a January 2011 company overview of its portfolio, and the company recently highlighted progress on some of those candidates. In January 2011, GSK started two global Phase III studies in patients with advanced or metastatic melanoma that have a BRAF V600 mutation. The studies will separately assess the efficacy and safety of two investigational agents, GSK2118436 and GSK1120212, to determine their individual ability to stop or slow the progression of skin cancer in patients whose tumors contain a BRAF V600 mutation, which the company said occurs in 50–60% of melanoma patients. GSK also will evaluate these compounds alone and in combination with other agents in other difficult-to-treat forms of cancers, including pancreatic cancer, refractory or relapsed leukemia, and other solid tumors.

Also in January 2011, GSK received a positive recommendation from EMA for Trobalt (retigabine) as an adjunctive treatment for partial onset seizures (i.e., a form of epilepsy where a seizure begins in a specific area in one side of the brain), with or without secondary generalization in adults aged 18 years and older with epilepsy. Retigabine received preliminary approval from the Swiss Agency for Therapeutic Products, Swissmedic, in December 2010. Retigabine, referred to as ezogabine in the US, is being jointly developed by GSK and Valeant.

GSK also began Phase III studies for GSK2402968, an antisense oligonucleotide, to treat a neuromuscular disease, Duchenne muscular dystrophy in ambulant boys who have a dystrophin gene mutation amenable to an exon 51 skip. The drug was granted orphan-drug status in the EU and US and is being developed as part of an alliance between GSK and Prosensa.

**Roche**. Roche's late-stage pipeline includes potentially 10 regulatory submissions of NMEs through the end of 2013, according to a Dec. 9, 2010, Roche press release Some key compounds are T-DM1 (trastuzumab) and pertuzumab for treating breast cancer and GA101/RG7159, a glyco-engineered Type II humanized anti-CD2-monoclonal antibody to treat relapsed/refractory aggressive non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Aleglitazar is being developed to treat cardiovascular risk in patients with Type II diabetes, and dalcetrapib is being developed to reduce cardiovascular risk and dyslipidemia. RG1678, a glycine-reuptake inhibitor, is being developed to treat the negative symptoms and suboptimally controlled positive symptoms of schizophrenia.

Roche also is evaluating the progress of late-stage compounds to move them either to Phase III development or possible registration. Some compounds include RG7204, which is designed to selectively inhibit the mutated BRAF protein, which can be found in certain cases of metastatic melanoma. MetMAB, a monovalent antibody, is being developed to treat solid cancers. Ocrelizumab, a humanized anti-CD20 antibody, is being studied to treat multiple sclerosis, and RG7201 and taspoglutide are being examined as treatments for Type II diabetes.

**Bristol-Myers Squibb**. Bristol-Myers Squibb pointed to five key potential product approvals in 2011 based on a company overview presented in January 2011. These candidates include ipilimumab, an anticancer immunotherapy; belatacept, a co-stimulation blocker developed as an alternative therapy in solid-organ transplantation; apixaban, an oral Factor X inhibitor as an anticoagulant; dapagliflozin, an antidiabetes treatment; and a subcutaneous formulation of Orcenia (abatacept) to treat rheumatoid arthritis. The company also highlighted four drug candidates that potentially may move to Phase III development in 2011. These drugs include: elotuzumab, a humanized monoclonal antibody to treat multiple myeloma; a peptide functioning as a gamma secretase inhibitor to treat Alzheimer's disease; PEG-IFN lambda, an interferon to treat hepatitis C; and a small-molecule NS5A inhibitor to treat hepatitis C.

**Other companies**. AstraZeneca had 10 NMEs as drug candidates in late-stage development (Phase III or in registration) and 12 products being developed as line extensions as of July 29, 2010. Merck & Co. reported on its research pipeline as of Oct. 22, 2010, which included 19 programs in Phase III development. Eli Lilly reported as of October 18, 2010, that it had eight drug candidates in Phase III development and three drugs under regulatory review. One recent setback reported by Eli Lilly on Jan. 12, 2011, was a recommendation of a FDA advisory committee for nonapproval of liprotamase, an oral, nonporcine pancreatic enzyme-replacement therapy for treating exocrine pancreatic insufficiency. The committee had questions about the degree of efficacy of liprotomase and recommended additional studies to be conducted before approval.

## Looking ahead

As companies navigate late-stage development, they face moderate industry growth in 2011. The global pharmaceutical market is expected to grow 5–7% in 2011 to reach $880 billion, slightly better than the 4–5% growth in 2010, according to estimates by IMS Health in October 2010. Five potential blockbuster products—defined as those exceeding $1 billion annually in peak sales—are expected to be approved and launched globally by the end of next year, projects IMS. In 2011, products with sales of more than $30 billion are expected to face generic competition in the major developed markets. **PT**

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# Common Deficiencies in Abbreviated New Drug Applications

## Part 3: Control of the Drug Product and Stability

Aloka Srinivasan, Robert Iser, and Devinder S. Gill

**Chemistry reviewers in the US Food and Drug Administration's Office of Generic Drugs provide Part 3 of an overview of common deficiencies cited throughout the Chemistry, Manufacturing, and Controls section of abbreviated new drug applications (ANDAs).** The reviewers aim to assist ANDA sponsors in building quality into their submissions by clarifying components of the applications.

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As part of the FDA's Office of Generic Drugs' (OGD) ongoing effort to streamline the review process and reduce the number of deficiencies cited for the applications, a series of articles are being published to provide transparency and clarity to applicants submitting applications in the Question-based Review (QbR) format. The articles highlight the need and significance of science based justification in establishing drug substance (DS) and drug product (DP) specifications, in-process controls for both DS/DP, choice of formulation, selection of a product design and selection of the manufacturing processes. Part 1 of this series, which dealt with the deficiencies cited in the drug substance section, was published in January 2010 (1). Part 2 of the series dealing with drug product composition and excipients was published in August 2010 (2).

The current article is intended to provide clarification with respect to intent and criticality of common deficiencies cited in the control of the drug product (3.2.P.5) and stability (3.2.P.8) portions of abbreviated new drug application (ANDA) submissions using the Common Technical Document (CTD) and Question-based Review–Quality Overall Summary (QbR–QOS) format as a guide. Please refer to the sidebar for a list of some of the deficiencies and comments. This is not an all inclusive list of comments and deficiencies pertaining to the drug product specifications and drug product stability, but includes questions that are cited frequently.

### 2.3.P.5 Control of the drug product*

The P.5 sections of the QbR–QOS and the body of data, in submitted ANDAs, should include all the proposed controls for routine analysis of the drug product batches including the proposed specifications, analytical methods with associated validations, batch analysis data for exhibit batches, and justifications for all proposed criteria. Much of the information provided in this section is relevant to both release testing (P.5) and stability or shelf-life testing (P.8). We will address the stability section later in the article.

The QbR–QOS includes two sets of questions with respect to control of the drug product. The questions are as follows:

- What is the drug product specification? Does it include all the critical drug product attributes?
- For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

The intent of the first set of questions is for the applicant to provide the specifications for routine release testing of the drug product; and to ensure that all critical drug product quality attributes are included in the specifications. The critical quality attributes (CQA) are linked to the intended use, function and performance of the product and are chosen based on the desired quality target product profile (QTPP). The CQAs may be based on compendial specifications and/or the attributes of the reference listed drug (RLD); and also information in the associated labeling. Development studies may be conducted by the ANDA holder to assure that the drug product meets the attributes of identity, purity, potency, assay, and quality. Examples of typical CQAs for solid oral and solution dosage forms are provided in ICH Q6A (3) and the QbR–FAQ (4).

Specifications are defined per ICH Q6A as "a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use"(3). Based on this definition, the typical information provided is a table or list of proposed tests, acceptance criteria, and analytical procedures for the drug product analysis. An all too common deficiency, which should always be avoided, is related to inconsistencies in the specifications listed in the QbR–QOS (CTD module 2.3) versus the body of data (CTD module 3.2). It is imperative that the two sets of specifications match. If there are differences, the CMC reviewer will be unable to ascertain which of the specifications are the final proposed product controls. The information provided in the QOS should be a summary of the detailed information found in the body of data.

The remaining comments and deficiencies will fit into specific categories related to drug product controls including impurities and degradation products, specific controls for specific dosage forms, and analytical methods.

**Impurities/Degradation products.** There are a number of common deficiencies with respect to impurities and degradation products in the drug product. These include inappropriate criteria and unacceptable justifications.

With respect to setting justified specifications, a commonly cited deficiency is related to control of process impurities in the drug product. In many cases the recommended ICH Q3B (R2) (5) qualification threshold (QT) is used for all specified impurities. This may be appropriate for degradation products; however, it is not appropriate for impurities that are solely linked to the drug substance synthetic route (i.e., process impurities). The drug product limits for a specified impurity that is process impurity should be set at no higher than that proposed in the drug substance limit.

Poor justification for the proposed degradation product is another common area where deficiencies are being cited. There are a number of ways to justify specified degradation product criteria including the following, which are not reported in any specific order:

- Specified impurity limits are in-line with *US Pharmacopeia (USP)* monograph criteria for specified impurities.

- Acceptance criteria are in-line with the qualification threshold (QT) recommended in ICH Q3B(R2) and *ANDA Guidance: Impurities in Drug Products* (draft) (5, 6) as long as there are no safety concerns. The guidance for calculation of the QT using recommended percentage or total daily intake of specified impurities, whichever is lower, should be followed.
- Qualification of the proposed criterion may be based on the following:
  - Level of impurity observed in the reference listed drug (RLD). Data from multiple batches of the RLD at or near expiration date may be provided for qualification.
  - Significant human metabolite of drug substance. Literature references should be provided to verify that the compound is a significant human metabolite.
  - Scientific literature: as long as there are no safety concerns with respect to the intended use.
- Impurities that are structural alerts for genotoxicity need to be controlled at the Threshold of Toxicological Concern (TTC) of 1.5 mcg/day, as found in the European Medicines Agency (EMA) and draft FDA guidance (7, 8). However, a higher limit may be proposed based on safety studies demonstrating that the proposed limit does not pose a safety concern. These studies are typically consulted to reviewers in the Pharmacology–Toxicology division.

With respect to unspecified impurities the proposed limit should be equal to or below the recommended ICH Q3B (R2) identification threshold (IT) based on the maximum daily dose. Please be informed that in most cases when a *USP* monograph includes a limit for "any impurity" or "any other impurity" for unidentified impurities it is recommended that the IT be used for the criterion instead of the monograph limit.

An additional area that may lead to a deficiency is the setting the same criteria in both the release and stability specifications for a degradation product, where there is an increasing trend during stability studies. If an upward trend is observed, it is recommended that the criteria in the release specifications are set tighter so as to provide better quality assurance that all manufactured batches meet the regulatory criteria throughout the product life cycle.

**Stereoisomeric drug products.** This is a class of drug products which has been gaining ground over the last two decades. With great strides made in the field of analytical separations and also chiral reagents, use of a specific enantiomer is becoming more of a norm in the field of pharmaceuticals. Insufficient information in the application may lead to deficiencies being cited.

There are two significant guidance documents which may be followed regarding chemistry and manufacturing controls for stereoisomeric drug products, Development of New Stereoisomeric Drugs (9) and ICH Q6A (3). Decision Tree 5 in ICH Q6A summarizes the requirements for the chiral drug substances and drug products.

**Control of the chiral impurities.** It is preferable to include controls for the enantiomer and also diastereomers in the drug product within

the constraints of sensitivity of the analytical procedure, unless adequate pharmaceutical development studies demonstrate that racemization or epimerization is not a possibility during the manufacturing or storage of the drug product. The limits for the chiral impurities may be justified by comparison with the RLD product, published literature or safety studies.

**Chiral assay.** In cases where racemization is found to be insignificant or a very small amount of chiral impurities are expected to be present, a non-chiral assay may be considered sufficient as a control. However, if the active pharmaceutical ingredient (API) is prone to racemization or formation of other diastereomers during the manufacturing or storage of the drug product, a chiral assay is preferable.

**Stereospecific identity.** The agency's guidance, *Development of New Stereoisomeric Drugs* (9), states that drug products which contain enantiomers should have a discriminatory identification test. This is especially important when the racemate of the API is present in an approved drug product. Under such circumstances, a stereospecific identification test is requested, as it clearly demarcates between the enantiospecific drug product and the one containing a racemate.

Another scenario in which a stereospecific identification test is desirable is when the drug substance is prone to racemization under the proposed manufacturing process and storage conditions of the drug product.

**Additional issues with drug product controls and information.** The following is a discussion of other common deficiencies that are related to inadequate controls or justifications and missing information with respect to the drug product.

**Identification.** Identity testing of the drug product is a required quality requirement, as well as, a cGMP requirement (10). Most products include a satisfactory test for identity; however, there are cases where deficiencies have been issued based on the fact that another identity test may be necessary, if the proposed identity test is non-specific. In some cases a specific identification test is required, especially when there is a possibility of conversion of the active ingredient into another form (e.g., another salt, polymorph, or stereoisomer) based on the process conditions or during typical storage.

**Color.** This control may be especially important for solutions. A quantitative control for color based on comparison with the innovator's product is desirable. A quantitative control for color is often requested for oral solutions and injections, especially where degradation of the API may occur during storage; or where there is evidence that interactions of the API with the excipients, manufacturing equipment or interaction amongst excipients may cause a change in color of the drug product. Again, adequate pharmaceutical development studies demonstrating the absence of these interactions may justify not including a quantitative control for color for solutions.

**Reconstitution time.** For products that are intended to be reconstituted, such as powders for injection, a meaningful criterion for reconstitution time should be proposed. In many ANDA submissions this test is either not proposed or the limit is unreasonable based on the observed data, the RLD, or the intended use (e.g. for emergency administration). Most importantly, the limit should be based on a comparison with the RLD product. Additionally, ICH Q6A (3) states that test for reconstitution time can also be omitted based on development studies, however, these studies should be clearly referenced in the appropriate P.5 section.

**Disintegration.** Many submissions include disintegration limits that are not reasonable based on the data and also the intended use. In general, if disintegration testing is included in the drug product release specifications, the criteria should be based on data generated from analysis of the exhibit batches. Also the disintegration time in release and stability should be commensurate with that proposed in the in-process control during manufacturing of the drug product.

If the product is an Orally Disintegrating Tablet (ODT), it is recommended that, in most cases, a criterion of NMT 30 seconds is proposed based on the current guidance (11). However, a higher criterion may be allowed for disintegration time if justified based on comparison to the RLD.

**Scoring.** It is generally required that the scoring configuration of generic tablets be the "same as" that of the reference listed

## Examples of commonly cited drug product and stability deficiencies and comments**

1. The specifications of the drug product provided in the QbR–QOS and the body of data do not match. Please clarify your proposed release and stability specifications for the drug product.

2. The limit for specified impurity X in the drug product is not acceptable as it is listed as a process impurity and should be controlled at no higher than that proposed in the drug substance. Please revise or justify.

3. Impurity X is a known degradant of the drug product and its level is increasing during shelf life. Thus we request that you set tighter limit of this impurity in release to assure the meeting of regulatory criteria during shelf life.

4. The limit proposed for Impurity X in release and stability of the drug product is wider than that recommended by ICH Q3B (R2) qualification threshold. Please tighten the limit or justify the proposed limit based on analysis of several lots of RLD, close to expiration date.

5. In view of the chiral nature of the active pharmaceutical ingredient in your drug product, we request you to include controls for the enantiomer and the relevant diastereomers. We also request you to include chiral identification as a routine release test.

6. We request you to include a quantitative control for the color of your drug product with adequate justification.

7. Please establish a criterion for reconstitution time based on a comparison with the RLD product.

8. Your proposed disintegration time in release and stability is different from that proposed in the in-process control during the manufacturing of the drug product. Please revise or justify.

9. Based on the fact that your tablets are scored, please submit data demonstrating uniformity of dosage on each half of the tablet. Please also submit data to demonstrate that the score depth is suitably to evenly split the tablets.

10. Please justify the proposed water content criteria in the drug product release and stability specifications and the also provide the reason for relaxing the criterion for stability samples compared to release.

11. The formulation for your drug product contains significant amounts of excipients which make it susceptible to microbial growth. Thus, we request that you include microbial controls for the release and stability of your product. Alternatively, you may conduct a one time test for water activity on stability samples of the drug product or demonstrate by a suitable method that your formulation does not support microbial growth.

12. Based on the formulation, please include a control for the osmolarity of the drug product based on comparison with the reference listed drug product.

13. Please include a control of p-hydroxybenzoic acid in the release and stability specifications of the drug product in view of the fact that methylparaben has been used as a preservative in the formulation.

14. Please include a justified control for viscosity and redispersibility of your oral suspension.

15. In view of the fact that the formulation of your oral suspension has shown a tendency of crystal growth on storage, we recommend a control of particle size during analysis of release and stability samples.

16. Please add controls in the release and stability specifications of your multilayer tablet, to ensure the tablet integrity over shelf life.

17. Please provide results of analysis of all exhibit lots of the drug product.

18. The label for the reference listed drug states that the patient may dissolve the drug product completely in one teaspoon of water in one minute and drink it. Please provide information to establish that your product meets this criterion. We recommend that a control be introduced in release and stability to ensure that the drug product is completely dissolved in water in one minute throughout the product shelf life.

19. Please provide information that the process impurities, possible in the drug substance, are separated from the parent peak and other degradants in your methods related to the drug product.

20. Based on Division of Bioequivalence recommendation regarding the dissolution specification, provide revised specification for drug product release and stability testing, a revised certificate of analysis and revised stability data sheets to reflect the recommended dissolution method and specifications. We also request you to test the third month accelerated stability samples to establish that your product meets the proposed dissolution specification.

21. You have provided comparative assay and impurity profiles between your product and the reference listed drug under accelerated conditions to justify your drug product release and stability acceptance criteria. Since accelerated storage conditions are not the normal storage conditions for the drug product, it is recommended that comparative batch analysis data be conducted at controlled room temperature conditions to demonstrate similar behaviors between your drug product and the reference listed drug.

22. Based on the fact that semi-permeable containers have been used in packaging of your drug product, please include a control for water loss in the stability specification.

23. Indicate any special studies conducted to support stability specifications such as data for drug product after constitution, combination with admixtures and/or under other conditions that occur when the drug product is administered according to the labeling instructions.

24. Based on the intended use, please provide information regarding any cycling studies (freeze-thaw and heat-cool studies) and photostability studies that were conducted for your drug product.

25. Please be informed that based on trends observed in the accelerated stability data, the expiry date for this product will be based solely on the accumulated full long-term stability data.

*** Comments are usually not deficiencies and are found in section B of deficiency letters*

drug. For more information regarding scoring requirement, please refer to the CDER MAPP 5223.2, Scoring Configuration of Generic Drug Products (12). Other sources of information regarding scoring may be obtained in British Pharmacopeia (BP) (13) and a recent USP stimuli article (14).

Applicants have frequently been asked questions based on the fact that the tablets are scored. In order to ensure the quality of the split tablets, information regarding uniformity of dosage based on content uniformity or weight variation on each half of the tablet is generally requested, based on drug load. Regarding the breakability of the drug product, applicants are often requested to provide the mass loss after splitting. In certain cases, where breakability is in question based on the shape and size of the tablet, the reviewer may also request the applicant to provide the score depth as a fraction of the tablet thickness. For modified release tablets with score, a one time demonstration of the comparability of the dissolution on whole vs. split tablets is recommended. The aforementioned studies on split tablets should be performed during product and

process development. As the dosage form becomes more complex, the necessity of routine testing during drug product release and stability analysis is more critical to the overall control strategy.

**Water content.** In many cases a control for water content is either not proposed or is poorly justified. An appropriate limit for water content takes into consideration contributions from the formulation components, the manufacturing process (e.g., a wet or dry process) and the product stability. The proposed limit should be reasonable based on the observed data for the exhibit batch(es). The criticality of the limit is heightened for products that contain API or excipients that are sensitive to residual moisture, which may lead to degradation or product performance issues.

**Microbiological controls–nonsterile products.** A common comment that may come from the Agency during the review is with respect to microbiological control for nonsterile products. Based on the formulation components (e.g., lactose, other sugars) and product's water content, it may be prudent to include standard microbiological tests including aerobic microbial count, total yeasts and molds or specific pathogens. In some cases data on water activity of the product can be used to justify not performing microbial limits testing. The term 'water activity' (aw) describes the (equilibrium) amount of water available for hydration of materials (15). Published literature shows that absolute limit of microbial growth is about aw = 0.6. Thus, pharmaceutical development studies showing the water activity of the formulation is below this level during typical storage may justify not including microbiological controls for non-sterile, solid oral dosage forms. Additional references for microbial testing for non-sterile products and water activity may be found in ICH Q6A and *USP* <1111> (3, 16); and *USP* <1112> (16), respectively.

**Osmolality/Osmolarity/Tonicity.** For injectables (especially intravenous products) comparison of osmolality/osmolarity to RLD should be provided. If the results differ, then justification may be needed. As buffer systems may be different based on 21 *CFR* 314.94(a)(9)(iii) (17), differences in the osmolality/osmolarity compared to the reference product may be observed. The applicant needs to address this difference, as noted in the CFR, which states that the difference in formulation should not affect the safety of the proposed product. If the acceptance criterion for osmolarity/osmolality is listed in the RLD labeling, it is recommended that it be included in the product specification.

**Antimicrobial preservative and antioxidants.** Antimicrobial preservatives and antioxidants may be essential for establishing an acceptable shelf life of drug products. Antimicrobial preservatives by preventing microbial proliferation and antioxidant by preventing oxidation of the API, as well as, the excipients. In a parenteral formulations, based on 21 *CFR* 314.94(a)(9)(iii) (17) an applicant may choose to substitute or add antimicrobial preservative or anti-oxidant based on adequate justification. The key term here is "adequate justification". On many occasions deficiencies are cited as the applicant may have failed to rationalize the proposed levels of the antimicrobial preservatives or antioxidants in the proposed drug product. Additionally, there have been instances where applicants have not provided substantial rationale for substituting or adding the antimicrobial preservative or antioxidant in a parenteral formulation, especially when the RLD product does not contain one or the other.

*USP* <51>, which deals with Antimicrobial Effectiveness Testing, clearly recommends the minimization and justification of the range and/or criteria proposed of antimicrobial preservatives (16). Similarly, the applicants need to justify the chosen level of antioxidant in the formulation. The level of antioxidants is preferably justified based on pharmaceutical development studies demonstrating the minimum level at which the required activity is achieved and supported by the stability data provided in the application. The finished product release and stability specification should include limits for any antioxidant or antimicrobial preservative present in the formulation. The controls should comply with the requirements in ICH Q6A (3).

In some cases, the applicants are also requested to control plausible degradants

in the antimicrobial preservatives and antioxidants. Some well known examples of degradants are benzaldehyde and benzoic acid in benzyl alcohol and p-hydroxybenzoic acid in methylparaben and propylparaben. The applicants may be asked to monitor these during routine drug product release and stability analysis. The justification of the criteria for these degradants, in most cases, is consistent with the justifications used for drug product impurities, noted previously.

**Rheological properties, redispersibility and particle-size distribution of oral suspensions.** There are often questions regarding the above attributes, especially in case of oral and injectable suspensions. The viscosity of a suspension is considered an important attribute, as it is reflective of the settling tendency of the particulate matters in the suspension. It is also an indicator of the ease of pouring a suspension from a bottle or injecting it through a needle (18). The controls should be based on studies that demonstrate that the tendency to segregate during the manufacturing and storage has been minimized and/or controlled. Suitable tests should be included based on comparison with the innovator's product or pharmaceutical development studies.

**Suspension stability and particle size.** Redispersibility is critical for oral and injectable suspensions if sedimentation occurs during the storage of the suspension. The acceptance criteria should be set based on an appropriate and reproducible method. The time taken for re-suspension should be defined, based on pharmaceutical development studies and have minimal intra and inter-lot variability.

Occasionally, crystal growth in pharmaceutical suspensions is known to cause a drastic change in particle size distribution, which in turn may affect the physical stability of the suspension and sometimes, the bio-availability. Thus, particle size distribution may be a critical quality attribute of some suspensions, which may need to be monitored at release and over shelf life. See also ICH Q6A and the QbR FAQ for additional information (3, 4).

**Multilayer tablets.** With respect to multilayer tablets, it is incumbent on the applicant to provide development studies and/or suitable controls to ensure tablet integrity. If controls or development studies are not provided, it is likely that applicants will receive a deficiency.

It is recommended that when an applicant develops a multilayer tablet, they should provide data on layer integrity (e.g., radial crushing test). Additionally, during development or through a control strategy the applicant should provided assurance that tablets, throughout the product lifetime, exhibit consistent cohesion. In some cases a routine friability test performed on stability samples may be sufficient.

As the tablet layer integrity may be contingent upon material attributes of the chosen inactive ingredients, if post-approval changes in supplier or grade change; the applicant should be prepared to demonstrate that tablets manufactured with a different supplier or grade of inactive ingredients show multilayer products of comparable quality and performance. This same line of thinking would apply to changes made to the manufacturing

equipment or process. Applicants may be asked to provide data to demonstrate that multilayer products of comparable quality and performance are manufactured. Additional considerations may be found in a recent article on multilayer tablets (19).

**Transdermal delivery systems and locally acting patches.** Although transdermal delivery systems (TDDS) and other patches are not currently common dosage forms, as these products become more popular deficiencies would be cited with respect to specific critical quality attributes (CQAs) if they are not addressed in the submission.

Adhesion is by far of the most critical attribute that should be addressed in applications. Product adhesion is a CQA related not only to product quality and performance, but to product safety. The applicant should be able to measure adhesion in the proposed product with an appropriate, justified test and they should be able to demonstrate that the proposed system shows consistent product quality, performance and safety in terms of adhesion. A good reference on the criticality of adhesion in TDDS is a recent review article (20). Additional literature and guidance is also available on critical attributes of TDDS and patches (21, 22).

**General drug product information.** There are a few pieces of general information that if not provided will lead to deficiencies. As stated previously, this is not intended to be an all inclusive list. Common information not provided in the ANDAs that has lead to deficiencies includes the following:

- Results for all strengths are not included.
- Quantitative results are not presented for numerical tests, but general terms such as "complies" or "meets limit" are reported.
- A *USP* <467> compliance statement along with option used is not included in the drug product specifications.
- In case of the drug product label having specific information regarding how the patient may use a drug product, additional controls may be requested in release and stability. For example, if the label of a chewable, dispersible tablet claims that it may be dissolved in water or juice completely before taking, a test may be needed to establish that the generic meets the same criteria.

**Methods and validations.** There are a variety of common deficiencies regarding the analytical methods used for the drug product analysis, as well as, the associated method validation studies. One common question cited to applicants is related to insufficient method information being provided in the QbR-QOS, especially for non-compendial methods. The applicant should provide a brief summary of each non-USP method. This can be in a tabular or descriptive form and the information should include the critical parameters for the method and system suitability criteria, if applicable. Specifically for impurity methods, it should be clear that impurities (degradation products) are quantified using impurity standards or by the use of relative response factors (RRF).

In some submitted ANDAs, inadequate method validation information is provided. For in-house methods, validation protocols should include all the relevant tests as noted in *USP* <1225>, including method robustness (16). Typical robustness testing in HPLC methods includes varying chromatographic conditions, chromatographic systems, and/or mobile phase preparations. If a method is transferred then some minimal verification testing should be provided including tests such as intermediate precision (ruggedness) and determination of limit of detection (LOD) or limit of quantification (LOQ), as applicable. Compendial methods may also need to be verified based on the proposed laboratories ability to perform the method. A good reference for method verification can be found in *USP* <1226> (16).

Some specific studies and information that is often lacking in submitted method validations reports include linearity studies that do not include the proposed limit or the LOQ; inadequate or irrelevant acceptance criteria in the validation protocol, and lack of spiking studies to assess method suitability for detecting specified degradation products that may increase over time. Additionally, stress studies often are insufficient to assess stability indicating nature of

the method as no degradation is observed in stressed samples. It is typically recommended to target 10–30% degradation in stressed samples. For molecules that are difficult to degrade, a justification should be provided along with a summary of forced degradation results (i.e., stress conditions that go beyond the usual) or other studies performed to demonstrate specificity (4).

### 2.3.P.8 Stability

The P.8 sections of the QbR–QOS and the body of data in submitted ANDAs include information with respect to stability studies used to determine the shelf-life of the product. As stated previously, much of the information provided in the P.5 section is relevant to both release testing (P.5) and stability testing (P.8).

There are three QbR–QOS questions noted in P.8. These are as follows:

- What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?
- What drug product stability studies support the proposed shelf life and storage conditions?
- What is the post-approval stability protocol?

This article will focus on the first two questions with respect to common deficiencies and comments cited in ANDA submissions.

**Stability specifications.** Based on ICH Q1A(R2) (23) stability studies should include testing of attributes of the drug product that are susceptible to change during storage and may influence quality, safety, and/or efficacy of the drug product. The testing should cover the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating.

**Modification of limits for stability.** In some cases, the relaxation of the limits of certain quality attributes in stability is necessary based on the nature of the drug product. Applicants should take great care in using realistic, as well as, scientific and regulatory approaches to setting acceptance criteria for the stability studies.

For example, when the API or one of the excipients is hygroscopic, the water content may increase during shelf life for solid oral dosage forms. Similarly, if a hydrolytic degradation pathway related to an API is well documented in literature, the resultant degradant may be controlled at a higher level in stability. This may also be the case with an impurity, which arises due to reaction of the API with one or more of the excipients in the dosage form. However, deficiencies are cited when the relaxation of the specification is not well justified.

In case of water content, in the example noted above, it needs to be demonstrated that the proposed relaxation is not detrimental to the product quality in any way, leading to change in appearance, physical attributes or impurity levels. In case of degradants, the relaxed limit is acceptable as long as it is within the ICH Q3B (R2) qualification threshold (QT) and the impurity is not a structural alert for genotoxicity. However, if a limit higher that the QT is proposed, it needs to be justified by comparison with several lots of RLD, close to or at expiration date. In case of artifacts arising due to interaction of the API with the excipients, the levels need to be at ICH Q3B (R2) proposed QT or adequately justified based on safety data.

**Accelerated stability data on RLD samples.** Deficiencies are often cited when the relaxation of specifications of impurities in stability is justified by comparison with RLD, which has been subjected to degradation under accelerated stability conditions. Since accelerated storage conditions are not the normal storage condition of the drug product, it is recommended that the comparative batch analysis is conducted at controlled room temperature conditions to demonstrate similarity of behavior between the RLD and the generic.

**Specific studies or tests on stability samples.**

**Water loss.** Per ICH Q1A(R2) (23), it is recommended that aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss during stability studies. Deficiencies have been cited with respect to applicants using semi-permeable containers with no evaluation of potential water loss. It is recommended that the ICH Q1A guidance approach be used with respect to performing studies under low relative humidity conditions. Alternative approaches to determine water loss based on differing stability conditions can also be used, per the guidance.

**Dissolution**. The responsibility of reviewing the adequacy of the dissolution specification rests with the Division of Bioequivalence (DBE). However, a frequent deficiency provided to the applicants is to update the drug product release and stability specification based on DBE recommendations. It is also imperative that the applicants conduct the dissolution test by using the DBE recommended method on retained 3rd month accelerated stability samples for all packaging configurations and ensure that the exhibit batch meets the proposed specification. If accelerated stability samples are not available, testing should be conducted on samples placed in controlled room temperature. In this case, typically, the age of the samples at the time of testing will be the tentative expiration dating period that OGD will grant to the drug product. As such, updated stability protocols should be provided reflecting the reduced tentative expiration date. To avoid the reduction of shelf life, it is recommended that samples, which have already been taken out from the accelerated stability study chamber be retained until approval of the ANDA.

**Photostability studies.** The information regarding photostability studies for the drug product is often absent from the application. As ICH Q1B (24) states, the studies on the photostability of drug product need to be done in a sequential manner, starting with the fully exposed product and proceeding, if necessary to the immediate pack and then to the marketing pack, until results demonstrate that the drug product is adequately protected from exposure to light. In some cases, the ANDA holder justifies not performing photostability studies for the drug product based on the fact that the drug substance did not show photo-degradation during the forced degradation studies. However, this is may not be acceptable, in some cases, since the excipients or impurities there in, may catalyze photo-degradation of the API in the drug product. In these cases the applicant will need to scientifically justify why photostability studies are not necessary.

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Alternatively, if the applicant demonstrates that the generic product packaging provides a comparable level of protection to the RLD packaging, photostability studies may be exempted.

**Thermal cycling.** Thermal cycling studies or freeze-thaw cycling studies are recommended for certain dosage forms such as solutions, suspensions and emulsions to ascertain the effect of extreme temperature fluctuations during shipping through various climatic zones, seasonal fluctuation in temperature and mode of transport on the physical stability of the drug products. These studies are generally desirable for those drug products which may undergo phase separation, loss of viscosity, precipitation, and change in particle size distribution. However, we frequently see deficiencies cited in the ANDA due to lack of thermal cycling studies. It is desirable that the ANDA holders carry out thermal cycling studies during product development to assure a robust formulation. Also, a one time thermal cycling stability study needs to be conducted on the exhibit lot of the drug product to verify its physical stability, when applicable.

**Diluent studies.** Stability testing of the pharmaceutical product after constitution or dilution, where applicable, should be conducted based on the information in the labeling of the RLD. This testing should be performed on the constituted or diluted product through the proposed in-use period on exhibit batches as part of the ANDA submission.

**Accumulated data/studies.** Usually, satisfactory results of three months accelerated studies justify a tentative expiration date of 24 months. However, based on trends observed in the accelerated stability data, the expiry date for some products may be based solely on the accumulated full long-term stability data.

There are drug products, due to their inherent nature show a significant change during the accelerated stability studies. In these cases, the expiration date is based on the long term stability data, though the ANDA holder may demonstrate that the RLD exhibits similar behavior under accelerated stability conditions. In cases were significant changes occur in accelerated conditions, applicants may also need to demonstrate (e.g., intermediate storage conditions) that excursions in temperature during routine shipping and storage have no detrimental impact on the product quality.

## Conclusion

This concludes our discussion on the commonly cited deficiencies for control of the drug product (3.2.P.5) and stability (3.2.P.8). This is by far the most active area when it comes to deficiencies and comments cited to ANDA applicants. The prevalence of deficiencies speaks to the criticality of the information with respect to controls proposed for routine release and stability analysis of the drug product. Applicants should endeavor to provide sound scientific and regulatory justification for all specifications (tests, methods, and criteria) that are proposed.

As stated in the beginning of the paper, this is not an exhaustive list of deficiencies in the drug product release and stability sections. However, the authors have attempted to provide the underlying reasons for common deficiencies related to the control of the drug product during release and stability testing. Our goal is to shed light on the rationale for citing these deficiencies and demonstrating how pharmaceutical development studies, performed during the initial development of the product, may reduce the instances of these deficiencies being cited.

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* Numbering in section heads correspond to those in the Common Technical Document (CTD).


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## Disclaimer

The views and opinions in this article are only those of the authors and do not necessarily reflect the views or policies of the FDA.

## References


1. A. Srinivasan and R. Iser, *Pharm. Technol.* **34** (1), 50–59 (2010).
2. A. Srinivasan, R. Iser, and D. Gill, *Pharm. Technol.* **34** (8), 45–51 (2010).
3. ICH, Q6A, Federal Register: 65(251) (Dec. 29, 2000).
4. FDA, QbR Frequently Asked Questions (June 4, 2007).
5. ICH, Q3B *Impurities in New Drug Products (R2)* (Geneva, July 2006)
6. FDA, OGD, *Guidance for Industry, ANDAs: Impurities in Drug Products (draft)* (Rockville, MD, August 2005).
7. EMA, *Guideline on the Limits of Genotoxic Impurities, Committee for Medicinal Products for Human Use (CHMP)* (Doc. Ref EMEA/CHMP/QWP/251344/2006), Jan. 1, 2007.
8. FDA, *Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (draft)* (Rockville, MD, December 2008).
9. FDA, Development of New Stereoisomeric Drugs (Rockville, MD, 1992).
10. FDA, "21 CFR 211 cGMPs for Finished Pharmaceuticals" [Testing and Release for Distribution, Sec. 211.165 (a)], revised Apr. 1, 2010.
11. FDA, *Guidance for Industry, Orally Disintegrating Tablets* (Rockville, MD, December 2008).
12. FDA, *MAPP 5223.2, Scoring Configuration of Generic Drug Products* (Rockville, MD, Nov. 1, 1995).
13. British Pharmacopeia, Formulated Preparations: General Monographs—Tablets Volume III, *Ph. Eur.* monograph 0478 (2010).
14. USP Stimuli Article, Pharmacopeial Standards for the Subdivision Characteristics of Scored Tablets, *Pharmacopeial Forum* **35** (6) (Rockville, MD, Nov–December 2009).
15. B. Snider, P. Liang, and N. Pearson, *Pharm. Technol.* **31** (2), 56–71, (2007).
16. *USP* 33–*NF* 28 (USP, Rockville, MD, 2010).
17. "21 *CFR* 314 Applications for FDA Approval to Market a New Drug," [Content and Format of an Abbreviated New Drug Application, Sec. 314.94 (9)], revised Apr. 1, 2010.
18. A. Gupta, V.A. Sayeed, and M.A. Khan, "The Science and Regulatory Perspectives of Pharmaceutical Suspensions," in *Pharmaceutical Suspensions, From Formulation Development to Manufacturing*, Eds. A.K. Kulshreshtha, O.N. Singh, G.M. Wall (Springer, New York-Dordrecht-Heidelberg-London, 2010), pp. 265–284.
19. S. Vaithiyalingam et al., *Internat. Jrnl. of Pharmaceut.* **398** (1–2) 2010
20. M. Wokovich et al., *Euro. Jrnl. of Phrm. and Biophrm.* **64** (1), 1–8 (2006).
21. FDA, *Guidance for Industry, Residual Drug in Transdermal and Related Drug Delivery Systems (draft)* (Rockville, MD, August 2009).
22. N. Sadrieh, B. Michniak-Kohn, and R. Harapanhalli, presentation at the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, Aug. 5, 2009, Topic 2, www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm178925.htm.
23. ICH, Q1A(R2) *Stability Testing of New Drug Substances/Products* (2003).
24. ICH, *Q1B Photostability of New Drug Substances and Products* (1996). **PT**

# Risk-Based Thinking in Process Validation

## Finding the Appropriate Number of Tests

James Agalloco

**The US Food and Drug Administration's draft process-validation guidance changes regulatory expectations by requiring manufacturers to validate their processes by performing enough tests to achieve statistical significance. The author describes why statistical significance, which industry had rejected, would impose an unreasonable burden on manufacturers and provide little, if any, benefit.**

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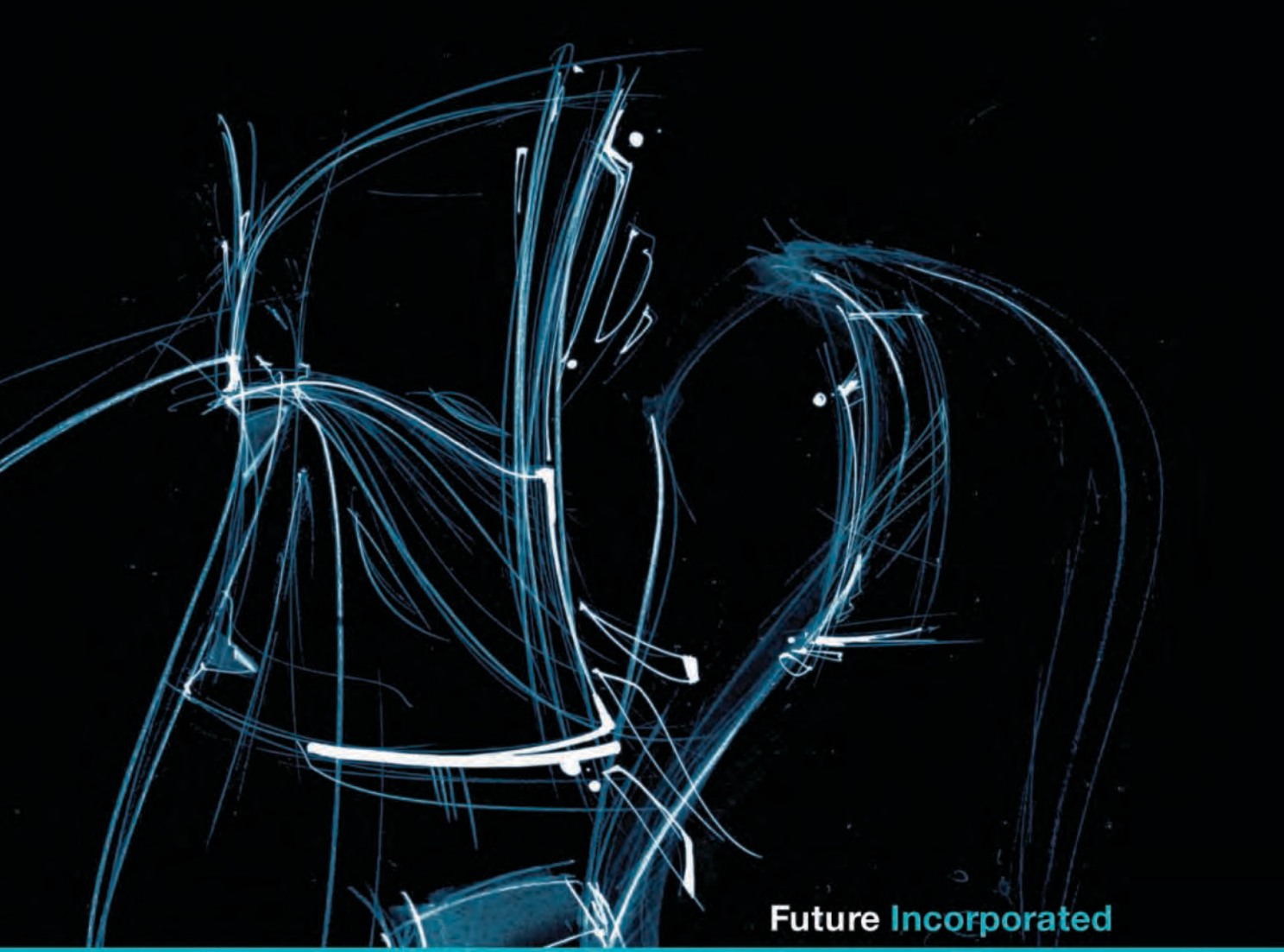
Validation has been practiced within the global healthcare industry since the early 1970s. While its exact origins are a matter of contention, during its evolution and unquestioned expansion into other areas, one element has remained unchanged during the past 40 years: an expectation of three performance-qualification runs. This practice was not always universal; before the US Food and Drug Administration issued its *Guideline on General Principles of Process Validation* in 1987, practice was somewhat more diverse (1). Interesting developments that emerged during the drafting and review of the original document have contemporary relevance to the 2008 draft revision of that guidance (2).

When the initial draft of the guideline appeared in the mid-1980s, it included an expectation for three performance-qualification runs as evidence of process control. When this document was issued for public comment, the organization that later became the Pharmaceutical Research and Manufacturers of America coordinated the development of a consolidated industry response. Some firms requested that the three-test requirement be reduced to two based on the premise that one replicate was sufficient to demonstrate process reproducibility. In an effort to accommodate all concerned, the responsible industry committee members developed a draft recommendation that the three-lot requirement be replaced with "a statistically significant number of batches." An almost immediate uproar came from companies that were performing three or more lots in their validation efforts. Although three trials were more than two, they certainly were not "statistically significant." When the organization realized this point, its members rapidly achieved a consensus on the three-trial expectation, and the comments that the group submitted on FDA's draft never mentioned the number of trials. Members acknowledged during those discussions that while "a statistically significant number of batches" would be more appropriate scientifically, the implications of such an approach were daunting.

This situation has now repeated itself, with the roles reversed. In its 2008 draft, FDA held that the "rule of three" is

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no longer appropriate and implied that more batches must be evaluated to provide the statistical confidence that is a central focus of the entire document. The difficulties inherent in expectations of statistical confidence in the 1980s are unchanged today. At a basic level, when the sample population is large, a sample size of 30 units generally is considered statistically appropriate. This output volume is actually quite substantial. During the author's 20 years of working in three large pharmaceutical firms, he encountered only six products (two parenterals, two active pharmaceutical ingredients, and two oral solid dosage forms) where more than 30 lots had to be produced in a single year. It should be immediately apparent that the initial validation of even relatively large-volume products cannot be accomplished using "a statistically significant number of batches." The time required to make the number of batches would be significant, and, in most instances, the material costs would be staggering. Validation efforts that extend for more than a few weeks are impractical from a logistical perspective, given the cost of drug-product manufacturing and the amount of inventory that must be held pending the completion of the exercise.

At the other end of the spectrum are low-volume products. These products are far more common than one might believe—not every product is a commercial blockbuster. The limited production volumes of these products may entail the manufacture of a single lot every 18 months or so. Validating low-volume products in a statistically meaningful fashion thus would require a 45-year period. Considering that future care might entail customized medications intended for a single patient, the total production of those products might consist of only a single lot. Clearly, using statistics to determine an appropriate number of commercial-scale lots to satisfy validation requirements is impractical.

## A risk-based proposal

What is to be done with respect to the extent of the initial validation under FDA's new guidance? FDA's Risk-Based Compliance initiative of 2004 incorporates some general precepts about how firms should use risk in defining and controlling their operations (3). Risk-based thinking has perhaps the greatest potential influence on validation. Performance-qualification protocols, especially as they relate to sampling size, sample location, and acceptance criteria, incorporate risk decisions throughout. The number of lots required for validation should be established through a risk-based approach to determining the number of trials required. Table I includes an example of a risk-based methodology applied to production processes for the completion of FDA's Stage II validation evaluation.

Although three or more batches are preferred for initial release, the distribution of products is permitted for any product after the successful production of a single batch. For processes that are new to the producer or heavily modified, extensive design of experiments (DOE) support is required in preparation for concurrent release.

The numbers listed in Table I are based on the following assumptions:

- These numbers are minimum requirements that could be increased when production demands and inventory charges permit.
- Relevant analytical methods are validated for all raw materials, solvents, excipients, in-process tests, and finished goods before process validation.
- Critical parameters for each process are predefined and controllable at scale-up.
- Phase I DOE experiments have been completed successfully for all critical parameters.
- Specifications and key characteristics are established and in compliance for all materials.
- All equipment is in a state of current qualification.
- Interim reports should be prepared for all materials released concurrently during the overall validation exercise.
- A single batch can be concurrently released with adequate prior development.
- In-process and finished-goods specifications are established based on documented experience rather than preconceived or arbitrary expectations.

The choices of specific numbers in Table I are arbitrary and based on the author's nearly 40 years of pharmaceutical-industry experience, which embraced all of these processes. In selecting the number of studies to perform in each instance, the author drew upon diverse sources for basic direction.

First, the process (i.e., process validation) and product are inseparably linked (4, 5). The process consists of the equipment chosen, the sequence of activities, the choice of materials, and the operating parameters. These items can be chosen independently to obtain the desired result. The result of the process is a product with unique characteristics (e.g., potency, uniformity, impurities, and moisture content). The product attributes depend on the process parameters used to make the product. The products' characteristics are the result of the process. If the process is altered in a meaningful way, the product key attributes also will be changed. Thus, the better defined the process, the more reproducible the result.

When a firm uses a process repeatedly, a substantial amount of useful data can be gathered for use when that same process is applied to different materials to produce a different product. For example, experience with tablet coating can be used for multiple products because the operating principles will remain constant, though the exact process parameters will differ. The amount of experience that a firm has with a particular process should be a factor in determining the number of Stage II validation batches necessary to demonstrate their capabilities.

Second, as is evident throughout the draft revision of the process-validation guideline, FDA expects manufacturers to acquire knowledge regarding the interaction between the independent process variables and the dependent product-quality attributes. The expectations for quality by design (QbD) are for the acquisition of knowledge regarding these relationships. The goal of the knowledge building is a minimization of risk in the

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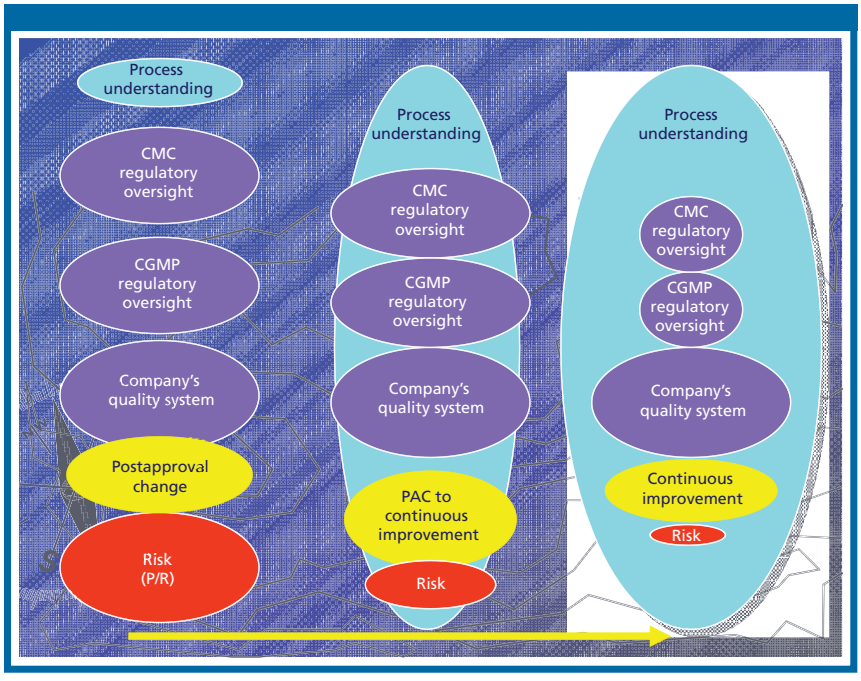


**Figure 1:** Process understanding and risk.

commercial production that follows the developmental effort. Although this goal was stated explicitly in the guidance, an even clearer picture was provided in FDA's first presentations about process analytical technologies, and later in presentations about the QbD initiative (see Figure 1) (6).

Third, the draft guidance appropriately emphasizes the importance of sound development during Phase I as the basis for a validated commercial process. Although QbD has become increasingly common, it would be safe to say that the majority of current products and processes have not been developed in a rigorous manner. When Stage I is performed as described, the scale-up and commercial demonstration exercise that follows in Stage II of the guidance entails an expectation that the exercise is more likely to be successful because of the increased process understanding and product knowledge the firm has gleaned from its developmental efforts. Under those circumstances, an extended Stage II demonstration with numerous lots might be of less benefit than it would when the development effort was weaker. Under the draft guidance, fewer Stage II batches are required because the process is more fully defined.

Fourth, the draft guidance has adopted a life-cycle approach to process validation in which the exercise is no longer considered an isolated activity, but one that is fully integrated into the development and commercial life of the product. This shift in thinking mandates a changed perspective on how validation is implemented and used in an environment in compliance with current good manufacturing practice (CGMP). The requirement for an annual review of product performance is a 21 *CFR* 211 expectation (7). In the author's experience, that activity was rarely linked to process validation in any meaningful way. Annual reports were largely isolated from the individual release decisions for a particular lot.

One means to address FDA's draft Stage III recommendations for continued process verification is to implement near real-time evaluation of results for commercial materials. With the increasingly available electronic tools of laboratory information-management systems, system control and data acquisition, among others, the results of testing for any lot can be rapidly compared with prior results for evidence of a shift in performance. This capability and expectation can substantially reduce the importance of the Stage II data. Although Stage II is important as part of the initial scale-up, it merely suggests future performance rather than predicting it. Release decisions in Stage III are made according to an even larger body of evidence, of which the Stage II results are only one part.

Fifth, when the 1987 process-validation guidance was issued there was an implied understanding that analytical methods should be validated. Methods and principles for that validation were not widely accepted, however, and the analysis was often labor-intensive. The ability to analyze samples in large numbers often was limited by the number of analysts available.* Process automation first appeared on the manufacturing floor, and is now found throughout the facility, including nearly all laboratories. Present-day laboratories are increasingly automated, which allows for the accommodation of larger sample sizes, higher throughput, and more timely and reliable results. Processes and products can be more effectively and expeditiously evaluated than ever before, and confidence in the results is substantially higher. As a consequence, Stage II lots can be characterized better than ever before, and added lots to build knowledge of process capability are not needed as much.

Last, and perhaps most importantly, Stage III of the validation life cycle lasts longer than any other, and the number of batches needed to make the transition from Stage 2 to Stage 3 is really not a significant factor. Maintaining a process in a validated state over its commercial life requires several supportive controls defined under CGMP regulations. The essential elements to support a product or process over its life cycle are change control (i.e., materials, procedures, test methods, and equipment), calibration, preventive maintenance, and person-

* The author has encountered numerous instances where the number of validation exercises that could be performed was limited by the laboratories' ability to analyze the validation samples in a timely manner. This was complicated by the sample numbers taken for purposes of validation that were many times the number used for routine release. These situations are far less common with today's automated analytical laboratories.

FIGURE IS COURTESY OF THE AUTHOR

**Table I: Phase II validation batch expectations.**

| One batch | Three batches | Five batches | Seven batches | Nine batches |
|---|---|---|---|---|
| • Simple changes to well-defined, immediate-release products<br>• Low-volume products (e.g., less than 5 batches per year). | • Immediate-release solid dosage forms with more than 10% active ingredient<br>• Nonsterile or sterile (i.e., powders or freeze-dried) solids with more than 10% active ingredient<br>• Oral or injectable solutions in an aqueous or solvent base<br>• Chemical-synthesis step using a named reaction<br>• Simple unit operations in chemical and biological processes relying on physical phenomena<br>• All other situations not listed in this Table. | • Immediate-release solid dosage forms with 1–10% active ingredient<br>• Nonsterile or sterile (i.e., powders or freeze-dried) solids with 1–10% active<br>• Oral, topical, or injectable gels in an aqueous or solvent base<br>• Chemical-synthesis step using a reaction or process previously validated by the firm. | • Immediate-release solid dosage forms with less than 1% active ingredient<br>• Sterile solids (i.e., powders or freeze dried) with less than 1% active ingredient<br>• Oral, topical, or injectable suspensions, creams, ointments, or suppositories<br>• Biological fermentation or cell-culture process similar to one previously validated by the firm. | • Modified-release dosage forms of all product types<br>• Novel chemical or biological synthesis processes |

nel training. These mechanisms support the acceptability of the product or process for the longest period, and the number of successful Stage II batches completed is largely irrelevant.

## Recommendations for Stage II

Considering the points that this article has examined, it would be inappropriate for the author not to take a definitive stance on the number of batches that should be required. The author believes that although cogent arguments for more batches exist in some instances for complex processes, perhaps equally good reasons indicate that increasing the expected number of batches across the board would create an unnecessary (and perhaps superfluous) burden in other instances. The author believes that essentially no change in historical practices is warranted. Three batches have served industry, FDA, and the patient well for more than 20 years. The suggested approach in Table I provides a risk-based approach that gives adequate consideration to the technical, commercial, and regulatory risks. The new guidance addresses that approach by requiring that firms develop a fuller understanding of their product and process and be thus able to support its adequacy without resorting to large numbers of Stage II studies.

## Validation as the scorekeeper

Personnel often blame the validation exercise when a process fails to meet its specified requirements. That blame is completely misplaced. Inadequacies in process-validation exercises are not associated with an inadequate number of batches as much as they are associated with inadequate science behind the process. Validation by itself is nothing more than an independent assessment of the inherent capability of the process. Just as one cannot test quality into a product, one cannot validate it in, either. FDA's draft guidance outlines a means for product quality and process reliability through reliance on sound science during process development. To the extent that Stage I is properly executed, process robustness is largely assured. The development activity seeks to gain knowledge about the product that will ensure its success in the clinic, and about the process that will ensure its suitability for that purpose. The later stages of the guidance outline means to transfer that knowledge initially into a commercial manufacturing environment and then support it throughout its time in the market. When firms fail to gain adequate knowledge initially and maintain it over time, they

are likely to encounter quality difficulties. The validation approach outlined in the guidance is intended to remedy that problem by mandating increased process understanding. Applying rigorous validation acceptance criteria or defining success criteria without adequate knowledge of the process or product capability misses the point entirely.

The premise of this article (and FDA's draft) is that as the firm gains process knowledge and applies it appropriately, the level of risk is reduced. Although QbD activities could be construed to be required to determine the independent parameter–dependent attribute relationship, the QbD exercise does not start with elemental science. Individuals will draw upon their educational backgrounds, and firms will rely on their prior efforts as the foundation upon which the new process and product is built. When that knowledge is extensive, the amount of new work required in the QbD exercise, and later in the commercial demonstration, should be reduced. Similarly, when the core process is simple, such as in the preparation of a solution, the amount of QbD or commercial-scale redemonstration of it should also be executed with less effort. The more knowledge a firm possesses, regardless how it has been acquired, should reduce the amount of new effort necessary in QbD or commercial-scale manufacturing. A well understood underlying process can serve to reduce the QbD and commercial-scale activities. Greater knowledge should lead to reduced risk.

The intent of this effort is to foster a dialog between industry and regulators that results in a shared understanding of regulatory expectations. The adoption of any specific value is not the intent of this proposal: the goal is to initiate communication that results in common ground on this subject, basing it on a risk-based model.

## Additional risk considerations

Validation of processes extends well beyond the direct production processes used for drug substances and drug products. The application of risk-based thinking in those activities makes sense for much the same reasons as it does for production processes. Extending the performance qualification for these processes beyond what already appears to be fully validated processes, however, has little apparent merit. For example, increasing sterilization validation, which is clearly an essential and critical process, beyond the current three-study expectation would not provide much benefit. The absence of validation-related problems with respect to sterilization across the industry suggests that added studies are not required. This result is in large part due to the robustness of the science applied to sterilization and the certainty of the operational controls. Considering the spectrum of nonproduction processes that require validation, those with greater risk are those with substantial quality implications where the underlying science is limited or process controls are less effective. At the other end of the spectrum are processes with minimal impact or with well defined and robust process controls. Thus, nonpro-

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**Table II: Risk categories for nonproduction processes.**

| Low-risk processes | Moderate-risk processes | High-risk processes |
|---|---|---|
| Automated systems | Sterilization | Manual cleaning |
| Water systems | Depyrogenation | Manual inspection |
| Process utilities | Automated cleaning | Aseptic processing |
| Automated inspection | | |

duction validated processes might fall into three major risk categories (see Table 2).*

The number of validation studies, the validation approach (i.e., concurrent or prospective), and, perhaps most importantly, the number of supportive background controls should all be dictated by the level of risk associated with the particular process. The author's suggestions are intended to provoke interaction rather than serve as definitive positions on the subjects.

One further concern relative to nonproduction processes bears repeating. FDA's draft guidance made no distinction between the direct and indirect processes within our industry. Although process validation may have derived from sterilization issues in the 1970s, the thrust of the 2008 draft guidance is heavily skewed towards direct production processes, and the document scarcely mentions the supportive processes, however important they might be. FDA should take a definite stance on the inclusion or exclusion of these supportive processes and system with respect to their final guidance (8). These processes would benefit from the same type of risk analysis outlined in Table I. The diversity of processes, however, would make consensus examples impractical, given the uniqueness of the individual processes.



## Conclusion

Validation is an essential and extremely useful activity within our industry (9). Its benefits may have been understood poorly, and thus understated for years. Nevertheless, interpreting or applying the guidance too restrictively can certainly result in a new wave of complaints regarding its proper role in pharmaceutical operations. One could easily assert that properly performed validation with good attention to scientific and engineering detail has always embodied the concepts of risk assessment and QbD since its inception. The FDA draft suggests that the "rule of three" will no longer suffice for future validation demonstrations at commercial scale, but the number of studies required should not be excessive.

Statistics certainly will play a large role in future validation studies. They should not define the number of studies required, however, lest they cause interminable delays and excessive cost. Validation, as redefined in the guidance, offers a means towards optimization and process economy, thus justifying the greater developmental effort required to achieve the desired state. Imposing excessive validation requirements on industry to attain that state on a commercial scale may not always serve a useful purpose. Given the renewed emphasis FDA is placing on process validation, it is essential that programs designed to meet it be fully compliant, and yet realistic with respect to the extent of the effort required. The adoption of a risk-based approach, as described in this article, affords perhaps a unique opportunity to accomplish both objectives at the same time.

## Acknowledgments

This paper was profoundly influenced by Phil DeSantis, Sr., director of engineering compliance at Merck Global Engineering Services; James Akers, president of Akers, Kennedy, and Associates; and Russell Madsen, president of the Williamsburg Group, each of whom played a substantial role in refining the author's opinions and developing this article.

## References

1. FDA, *Guideline on General Principles of Process Validation* (Rockville, MD, May 1987).
2. FDA, *Draft Guideline on General Principles of Process Validation* (Rockville, MD, Nov. 2008).
3. FDA, *Risk Based Compliance* (Rockville, MD, Sept. 2004).
4. J. Agalloco, *PDA J. Pharm. Sci. Technol.* **49** (4), 175–179 (1995).
5. J. Agalloco, *Pharm. Technol.* **32** (7), 70–78 (2008).
6. A. Hussain, DIA Annual Meeting (Washington, DC, 2004).
7. *Code of Federal Regulations,* Title 21, Food and Drugs (Government Printing Office, Washington, DC), part 211.180 (e)
8. J. Agalloco, *Pharm. Technol.* **33** (5) supp., s22–s27 (2009).
9. J. Agalloco, *J. Parenter. Sci. Technol.* **40** (6), 251–252 (1986). **PT**

* The categories of risk are associated with both patient safety considerations and process robustness (e,g., sterilization processes are high risk to the patient, but predominantly easily and reliably validated).


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# Addressing Segregation of a Low-Dosage Direct Blend

## During Commercial Scale-Up

Nipun Davar, Thomas Baxter, Pauly Kavalakatt, Sangita Ghosh, and Herbert Schock

**During the production of low-dosage tablets, segregation can cause variations in content uniformity. Fluidization during the transfer of ingredients from the blender to the bin, and then to the tablet press, could account for this segregation. The authors modified equipment and a manufacturing process to re-establish content uniformity among tablets. This article evaluates the results of those modifications.**

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Directly compressing a dry blend of pharmaceutical ingredients into tablets has the benefits of requiring minimal powder handling and reducing processing costs. Maintaining content uniformity of the dry blend, especially for low-dose therapeutics, throughout the process poses significant challenges. But personnel can modify the manufacturing equipment and process to help ensure content uniformity of low-dose tablets.

The authors produced a low-dosage tablet (i.e., one containing < 2% active ingredient) using a direct-compression process. The process included screening the drug along with the excipients, blending the ingredients in a V-blender, transferring the blend from the V-blender to an intermediate bin, and compressing the tablets using a 51-station D-Hata tablet press (Elizabeth-Hata International, North Huntingdon, PA).

Based on the process, an initial demonstration batch was manufactured at 787.5-kg scale. The proprietary composition comprised a low-dose drug, a carbonate buffer system, and coprocessed sugars as filler. Additional common excipients were included to aid in the tableting process. Given the low dose of the active ingredient, samples were collected and analyzed for blend uniformity (BU) and content uniformity (CU) per FDA's draft guidance for stratified in-process dosage-unit sampling (1, 2). The uniformity data were collected during various transfer steps and during compression. For the first demonstration batch, the BU data met the specification, but the CU results did not meet the specification: a location average exceeded 110% of the label-claim limit at the end of compression

To understand the lack of CU during the tableting process, the authors conducted several tests at the bench scale to elucidate the segregation mechanism and flow properties of the formulation blend. The authors hypothesized that fluidization during the transfer of the blend from the blender to the intermediate bin, and subsequently from the bin to the tablet press, could result in segregation of the active in the formulation.

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Based upon the test results described in this article, corrective process and equipment modifications were implemented for a second demonstration batch. These modifications successfully reduced the segregation during the blender-to-press transfer steps, so that the CU data passed FDA's draft guidance for the second demonstration batch (1). These modifications were incorporated into the commercial process and successfully validated. The details of the root-cause analysis and process and equipment modifications are discussed in the following sections.

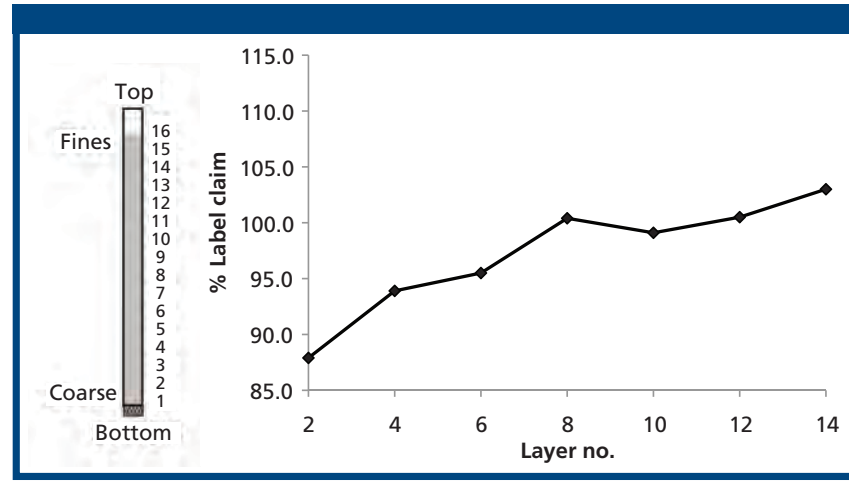


**Figure 1:** Fluidization-segregation test results showing drug content across individual layers.

## Root-cause assessment and confirmation

A root-cause analysis of the CU variation for the first demonstration batch was conducted using established troubleshooting methods (3). The BU data collected from the blender and bin had minimal variation and was within specification as described in FDA's guidance. The BU samples were obtained using a sampling thief from 10 locations within the V-blender and 12 locations within the bin. These samples weighed 1–2 times as much as the tablet. On the other hand, the CU data had higher variation (RSD = 3.2%, $n$ = 60 samples) due to a distinct upward trend at the end of compression (average = 112% label claim, $n$ = 3 samples).

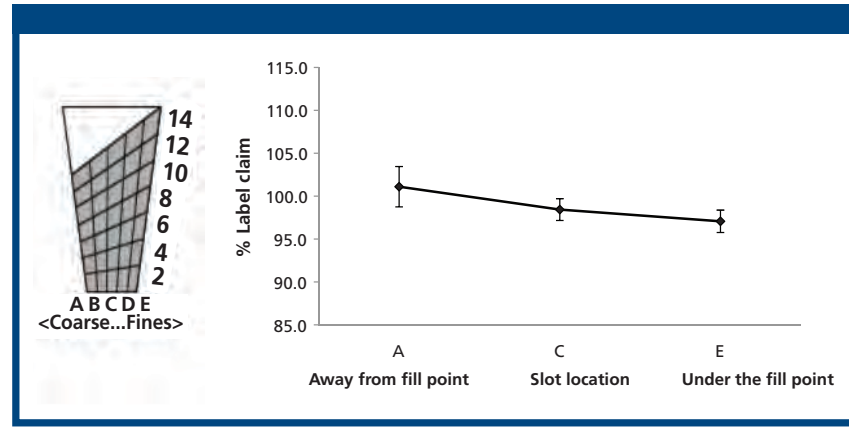


**Figure 2:** Sifting segregation test results showing drug content across slot locations.

During an analysis of variance of the CU data, the authors observed that more than 90% of the variation occurred between locations, as opposed to a variation of individuals at a single location. Samples collected from the intermediate bin also exhibited higher variation (RSD = 2%, $n$ = 12 samples) than the blender samples. Based on these results, the authors hypothesized that segregation during the postblending steps (i.e., the blender-to-bin or bin-to-press transfer steps), in combination with the flow pattern from the intermediate bin, resulted in the upward CU trending at the end of compression. In particular, fluidization with or without dusting segregation during the transfer steps can result in a concentration of active-rich fines at the periphery or top of the bin. When the segregated blend discharged in funnel flow (i.e., a first-in-last-out flow pattern), the drug-rich blend would be present in the tablets obtained toward the end of compression. The authors discussed changes in material flow patterns (i.e., mass flow versus funnel flow) and the effect they can have on CU trending in a previous article (4).

To confirm the root-cause hypothesis, bench-scale segregation tests were conducted to confirm the dominant segregation mechanism for the blend. A test was conducted on the blend to assess its potential to experience fluidization segregation. The test method, described in detail in the literature, is conducted by fluidizing a column of material by injecting air at the bottom of the test column, and allowing it to deaerate in a controlled manner (5). When the test is concluded, the column is split into 16 equal sections, and selected sections are assayed for drug content. If the blend were prone to fluidization segregation, samples from the bottom (i.e., Layer 1) would have a coarser particle size and contain a lower concentration of the drug than the samples from the top (i.e., Layer 14). The concentration of drug from the various layers from the fluidization segregation test data are graphically depicted in Figure 1. A trend of increasing drug concentration toward the top layers of the blend confirmed that the blend had a high tendency to segregate, predominantly because of fluidization.

Although fluidization was the primary factor, the authors performed a sifting segregation test by filling a narrow test

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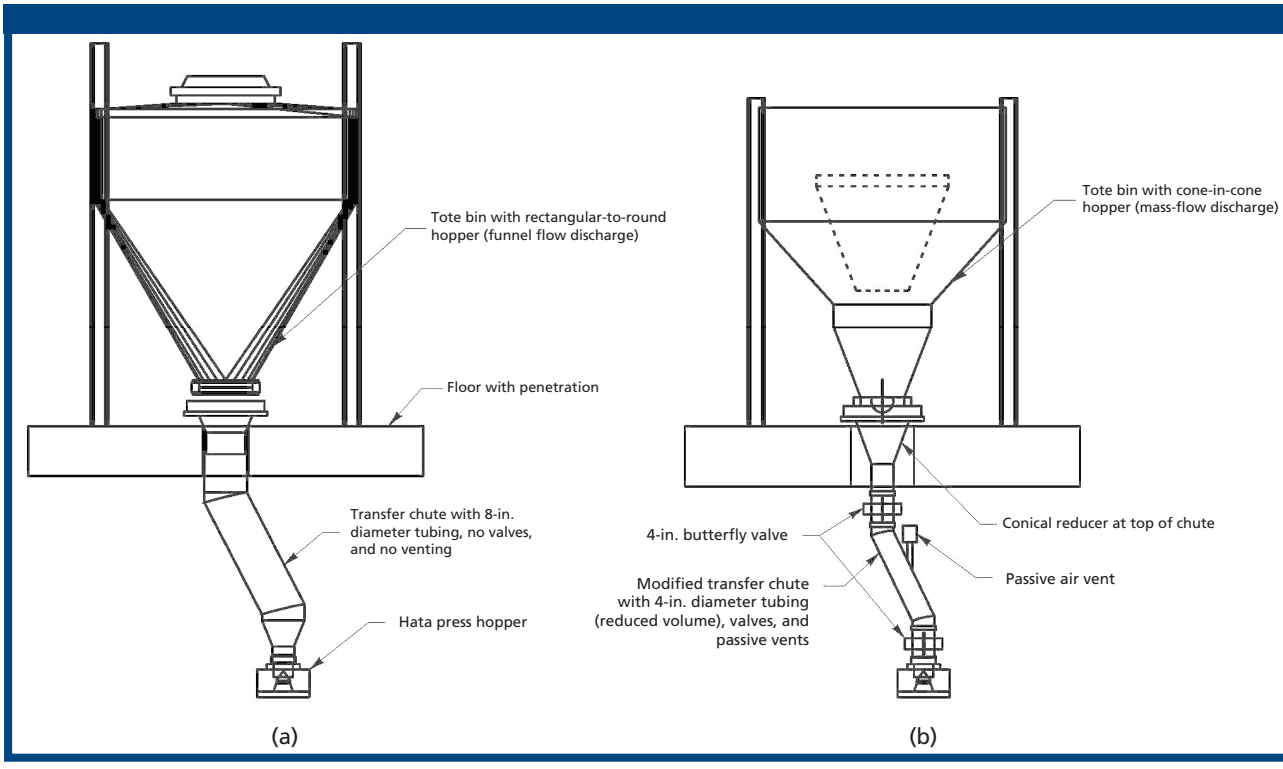


**Figure 3:** Tote-bin and transfer-chute modifications from (a) demonstration batch #1 in a bin-to-press feed system and (b) demonstration batch #2 in a modified bin-to-press feed system after process and equipment modifications.

cell to one side, thus allowing a pile of the dry blend to form within the cell. If a material segregates by sifting, the coarse particles flow to the far side, away from the fill point, while fine particles accumulate under the fill point. After the cell was filled, the samples were extracted from the bottom of the tester in layers, with a given layer subdivided into five slots. The first layer extracted was designated Layer 1, and as many as 14 layers were collected, depending on the surcharge angle of the material. Slot locations were designated A through E, with A being away from the fill point, and E under the fill point. If the blend is prone to sifting segregation, samples collected below the fill point (i.e., slot E) are drug-rich and finer than those collected away from the fill point (i.e., slot A). However, an increase in drug-rich fines away from the fill point (i.e., at slot A) is consistent with a fluidization or dusting segregation mechanism. The sifting segregation test data, as shown in Figure 2, demonstrated that the blend had a low tendency to segregate by sifting.

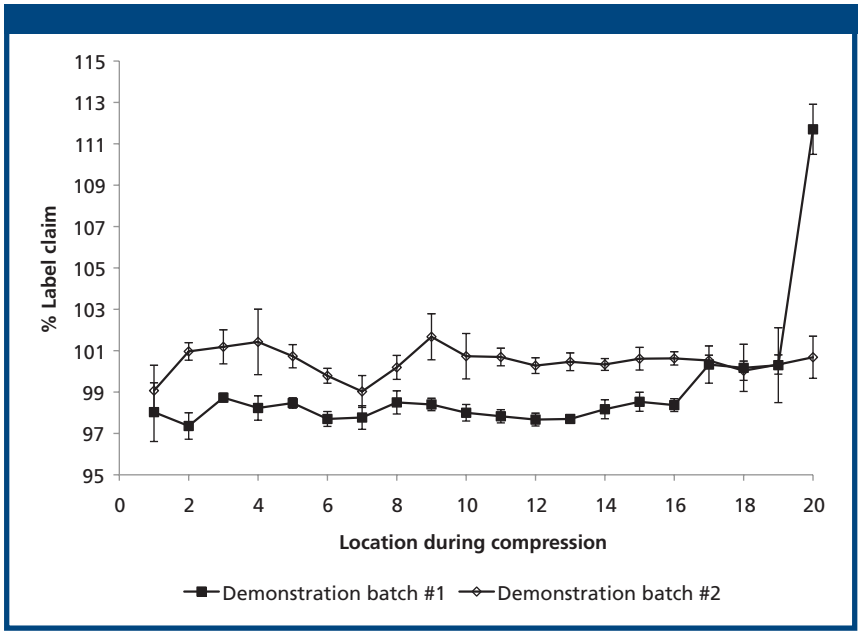


**Figure 4:** Stratified tablet content-uniformity data for (a) demonstration batch #1 with segregation and (b) demonstration batch #2 after process and equipment modifications.

The segregation test results confirmed that both the blender-to-bin and bin-to-press transfer steps could result in fluidization or dusting segregation, thereby leading to CU prob-

lems. Subsequently, flow-properties tests, including cohesive-strength and wall-friction tests, were conducted at the bench scale to confirm the flow pattern of the blend during the blender-to-press discharge (6). Based on the wall-friction test results, the authors concluded that the rectangular-to-round hopper angles for the bin used for the first demonstration batch were not smooth or steep enough to provide mass-flow discharge, and that the bin discharged the blend in funnel flow, thereby resulting in higher variation of the drug content in the tablets. Based on the flow-properties test results, a specially designed bin (i.e., a cone-in-cone) was used for the second demonstration batch. This bin design provided mass-flow discharge, thus minimizing the effects of dusting segregation during transfer.

## Process and equipment modifications

**Modifications to the blender-to-bin transfer step.** The blender-to-bin transfer step for the first demonstration batch consisted of an uncontrolled free fall from the blender into the bin, likely resulting in fluidization and dusting segregation. To reduce the likelihood of segregation during the blender-to-bin transfer step for the second demonstration batch, a flexible sleeve, or sock, was designed to control and reduce the transfer rate from the blender and minimize the free fall of the material during transfer. The customized sock had a conical section at the top that converged from the larger V-blender outlet (8-in. diameter) to a smaller diameter (i.e., 4 in.) to provide greater control of the material and reduce the free fall of material into the bin. In addition, the blender valve was throttled during discharge (as high as 10% open) so that the material could deaerate within the sock before the sock was lifted from the top surface of the material to transfer it into the bin. Based on the stratified blend samples collected within the bin after filling (RSD = 1.0%, $n$ = 10 samples), these process modifications were successful in minimizing segregation during this transfer step.

In addition to modifying the process equipment used for the blender-to-bin transfer step, the cone-in-cone bin was expected to provide mass flow and was used for the second demonstration batch. Visual observations of the material discharge from the bin during the second demonstration batch confirmed mass-flow discharge, as predicted by the bench-scale flow-properties tests conducted beforehand.

**Modifications during bin-to-press transfer.** Segregation also could occur during the bin-to-press transfer step and contribute to the CU trending observed in the first demonstration batch. The transfer chute used for the first demonstration batch consisted of large-diameter (i.e., 8-in.) tubing without any valves to reduce the free fall of material or venting to reduce the air counterflow up through the powder as the chute is filled. Since air counterflow during free fall as the chute is filled can result in fluidization and dusting segregation, thus carrying drug-rich fines back up into the bin above, a new transfer chute design was used for the second demonstration batch. The new transfer chute consisted of the following parts:

- A mass-flow conical reducer at the top of the chute and small-diameter (i.e., 4-in.) tubing to reduce the displaced air and counterflow during filling
- Two butterfly valves to reduce the free fall height during filling
- A passive filter vent to allow displaced air during filling to exit the chute rather than conveying back up through the blend and causing segregation.

The modifications to the bin and transfer chute design from the first demonstration batch to the second demonstration batch are shown in Figure 3.

## Results and conclusion

The process and equipment modifications implemented for the second demonstration batch were successful in reducing the CU variation and alleviating the upward CU trend that was observed at the end of compression in the first demonstration batch, as shown in Figure 4. The CU data for the second demonstration batch showed minimal variation (RSD = 0.9%, $n$ = 60 samples) and met the FDA draft guidance specifications. The successful validation of the commercial process further demonstrated the robustness of these modifications.

## Acknowledgment

The authors thank their colleagues Prasad Challapalli, senior scientist at Patheon; Jacques Mowrer, associate director of analytical chemistry, and Alicia Ng, analytical chemist, at Transcept; and Mary Thomas, former manufacturing-process engineer at Patheon for their collaboration on this project.

## References

1. FDA, *Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment* (Rockville, MD, Oct. 2003).
2. FDA, *Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment, Revised Attachments* (Rockville, MD, Nov. 2003).
3. J.K. Prescott and T.P. Garcia, *Pharm. Technol.* **25** (3), 68–79 (2001).
4. J.K. Prescott, and R.J. Hossfeld, *Pharm. Technol.* **18** (6), 99–114 (1994).
5. J.K. Prescott et al., *Pharm. Technol.* **30** (12), 54–64 (2006).
6. J.K. Prescott and R.A. Barnum, *Pharm. Technol.* **24** (10), 60–84 (2000). **PT**

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# FDA Obtains Sought-After PIC/S Membership

**Joey Gouws**

## Nearly six years after applying, FDA joins the Pharmaceutical Inspection Co-operation Scheme.

On Jan. 1, 2011, the US Food and Drug Administration Good Manufacturing Practice (GMP) Inspectors became part of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) family of GMP inspectors. FDA was invited to join as a Participating Authority at the joint meeting of the PIC/S Committee of the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) held in Malaysia last November.

Following the announcement of the invitation, Brenda Holman, executive director of strategic initiatives for FDA's Office of Regulatory Affairs (ORA), said, "One agency cannot inspect the whole world—we need collaboration and harmonization."

### Background and application process

FDA embarked on its long process toward PIC/S membership in June 2005 by submiting a formal application. The PIC/S assessement of FDA's application, led by an appointed rapporteur, focused on reviewing and evaluating the agency's GMP inspectorate quality system. In addition, a five-member delegation (representing five continents) from PIC/S conducted two assessment visits. The first visit, which lasted two weeks, included an assessment of the quality management system (QMS) at FDA headquarters as well as observation of two local GMP inspections. The second visit lasted one week and involved additional time at agency headquarters.

**Joey Gouws** is deputy registrar/director, Inspectorate and Law Enforcement, for South Africa's National Medicines Regulatory Authority, and second deputy chair of PIC/S.

Following the initial assessment visit, it was apparent to the PIC/S team that easy implementation of a QMS across FDA headquarters and its national field offices was hampered by the complexity and enormity of FDA operations. For example, the ORA office, which is responsible for inspections, has more than 3000 employees.

The first assessment report issued by PIC/S in January 2010 identified gaps on approximately one quarter of the PIC/S indicators. There are 89 indicators contained in the PIC/S audit checklist (see www.picsheme.org/accession.php for the list).

The FDA team involved in the application process worked diligently to meet PIC/S expectations and evaluation criteria before the assessment team's second visit in August 2010. The entire evaluation process of FDA took approximately 5 years. PIC/S has a maximum 6-year review period.

### Benefits of PIC/S membership

Drug regulatory authorities worldwide are faced with the reality of globalization, increased cross-border trade, counterfeit drugs marketed within and between countries, and constant progress and evolution in science and technology. Globally, significant resources are committed to actively support efforts to expand access to medicines in accordance with the leadership responsibilities of national governments and international regulatory agencies. PIC/S is designed to assist national regulatory authorities in strengthening their GMP inspectorate and regulatory standards.

PIC/S membership allows increased transparency and visibility of inspections performed by participating authorities, reduces multiple inspections of the same drug product or API manufacturing sites by different participating regulatory authorities, and increases the number of sites inspected globally. Membership enables more manufacturing sites to be monitored and reduces unnecessary duplication of inspections by national authorities. For example, inspection schedules are shared to identify sites of common interest. In addition, inspection coverage is coordinated in a manner that joint inspections can be performed, resulting in the more efficient use of resources and better harmonization of GMP guidelines, deficiency classification, and post-inspection communication of outcomes. Finally, members gain access to educational opportunities *via* joint-visits programs (this training program allows inspectors from different countries to observe others to determine similarities and differences in practice and interpretation of inspection routines), coach inspections, and PIC/S seminars and expert circles.

As the global pharmaceutical industry expands, collaboration is vital to regulators trying to oversee greater numbers of complex, multisite supply chains. However, it is acknowledged that GMP recommendations and legislation alone do not determine the success of quality assurance in practice. Quality (as a concept) and GMP compliance by the pharmaceutical industry are also dependent on effective implementation, appropriate enforcement, and a common interpretation and understanding of the GMP principles by the national regulatory authority's GMP inspectorate teams and by the regulated industry. **PT**

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# Changes Underway for Biopharmaceutical Outsourcing

**Eric Langer**

## More crucial biomanufacturing operations are expected to be outsourced in the near term.

Outsourcing has increasingly become synonymous with cost-cutting, even more so as the economic crunch has forced biopharmaceutical companies to evaluate virtually every budget line item. Despite improvements in the economy and corporate profitability, the preliminary data from BioPlan Associates *8th Annual Report and Survey of Biopharmaceutical Manufacturing* indicate that companies are continuing to focus on how to reduce costs (1). The shift in outsourcing of crucial functions may affect manufacturers' competitiveness in the long run.

For 2011, the BioPlan study finds that 1 in 10 biopharmaceutical companies has outsourced jobs in both process development and in biomanufacturing to reduce costs (see Figure 1). This outsourcing occurred at nearly twice the rate of research and development (R&D) job migration (i.e., outsourced by biomanufacturers at a rate of 7.2% and 4.6% to domestic and offshore vendors, respectively). All of these activities are considered core strengths for biologics companies, and when such jobs are outsourced, they tend to stay outsourced as institutional knowledge as infrastructure and experience migrate.

Outsourcing data from the BioPlan Associates' report are among the crucial manufacturing issues probed through the annual study of more than 300 global biomanufacturers and contract manufacturing organizations (CMOs). To put the data in context, this report provides a composite view and trend analysis from biomanufacturers in 35 countries. It covers capacity constraints, expansions, use of disposables, emerging trends and budgets, disposables, downstream purification, quality management and control, hiring issues, employment and training (1).

Current industry service suppliers are recognizing this shift and have begun adding capabilities to their offerings. "A number of CMOs are adding fill–finish capabilities as well as assay and product-characterization services to their offerings, and several are providing additional flexibility by offering clinical production in disposable bioreactor systems," said Don Durham, president of Durham Consulting in a recent interview with BioPlan Associates. Durham believes this reflects a continuing trend, and service suppliers are responding by adding business capacity in these support services.

### Outsourcing crucial operations

For the 2011 study, BioPlan Associates also evaluated the top 23 types of biomanufacturing operations currently being outsourced (see Figure 2). The survey showed, not surprisingly, that respondents outsourced an estimated average of 35% of their fill–finish operations. This level is consistent with last year's results. Approximately 26% of toxicity testing is being outsourced in 2011. In addition, outsourcing of both upstream and downstream operations (10.0% and 10.4% respectively),

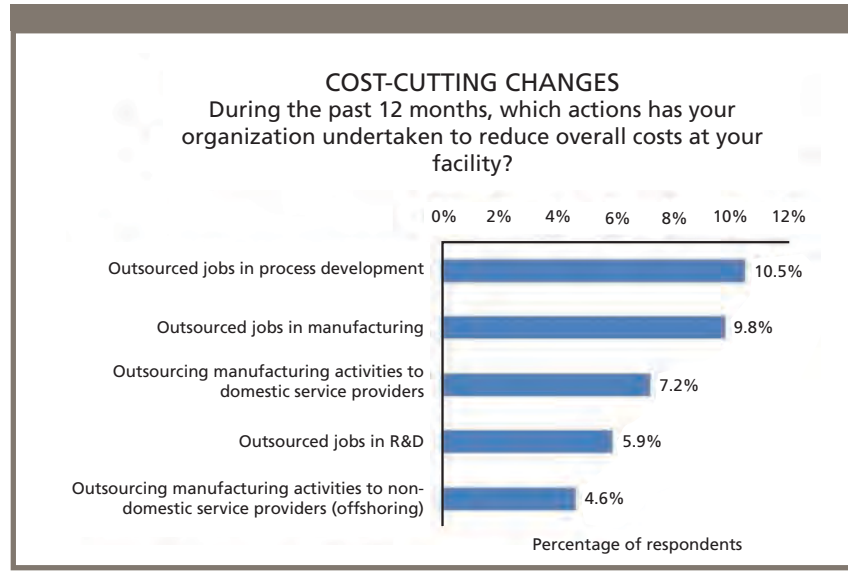


**Figure 1:** Percentage of respondents deciding to outsource select biomanufacturing functions due to cost-reduction efforts (1).

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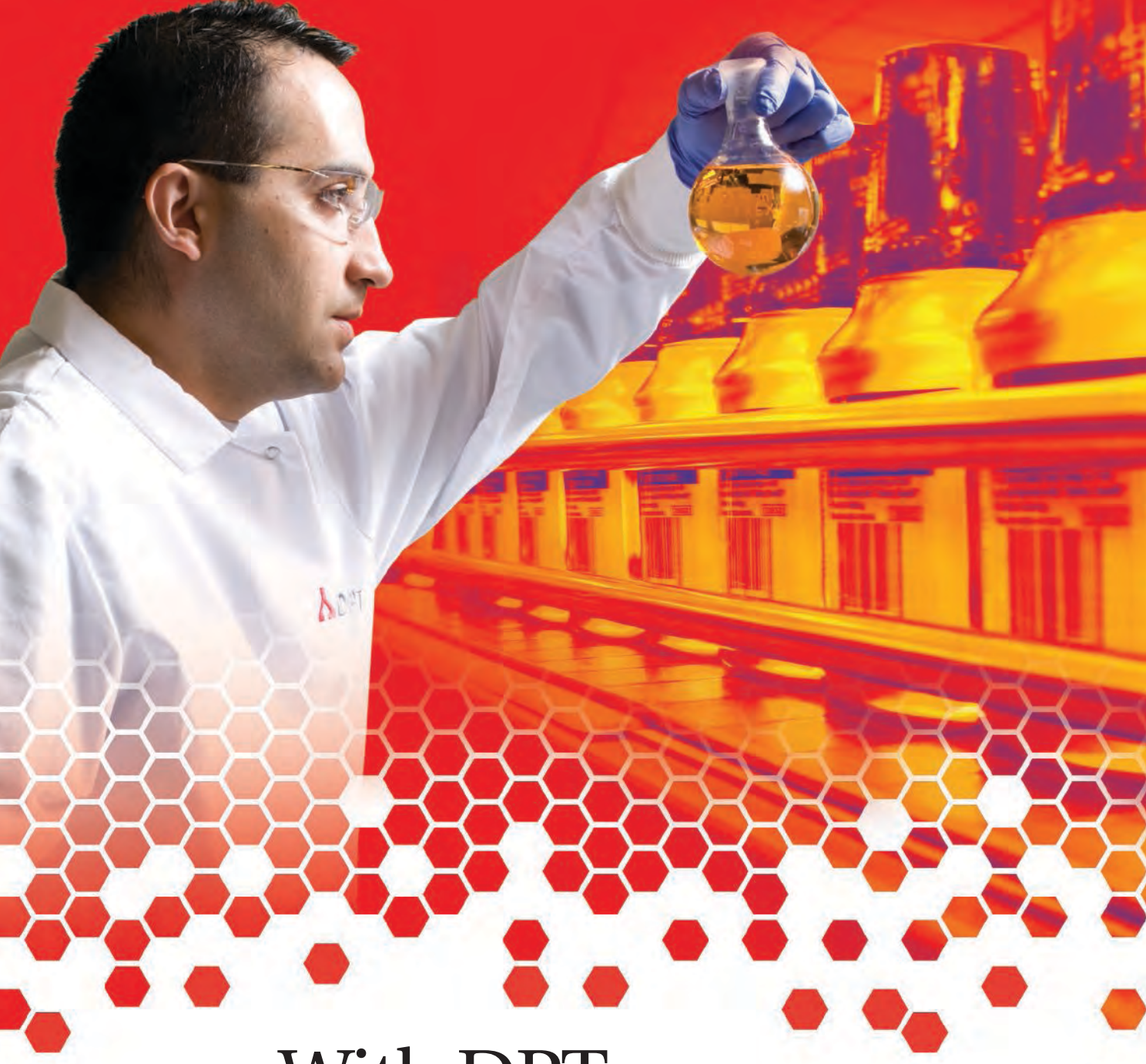
**Eric Langer** is president of BioPlan Associates, tel. 301.921.5979, elanger@bioplanassociates.com, and a periodic contributor to *Outsourcing Outlook*.



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DPT is the contract development and manufacturing organization (CDMO) that specializes in sterile and non-sterile semi-solid and liquid dosage forms. With unmatched technical expertise and fully integrated drug development and manufacturing services, we can help you successfully develop and commercialize your next product. Partnering with DPT gives you a seamless transition from pre-formulation to clinical supplies to commercial supply. After all, keeping it all together is what sets us apart. To get started, visit us at www.dptlabs.com or call 1.866.CALL.DPT.

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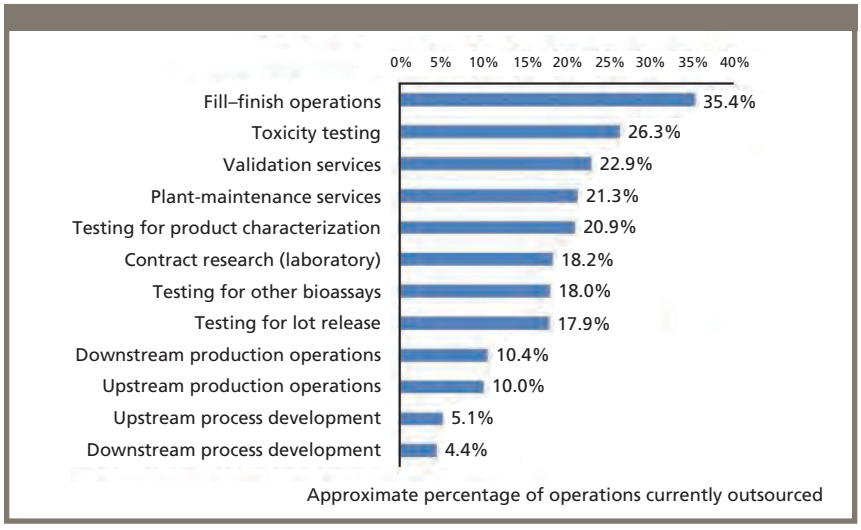


**Figure 2:** Estimated average percentage of outsourced activities by biomanufacturing facility (1).

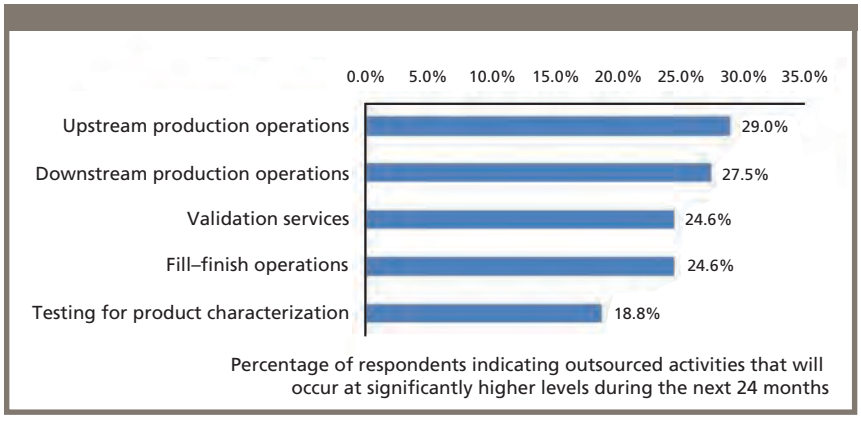


**Figure 3:** Respondents identifying biomanufacturing outsourcing activities likely to be done at significantly higher levels during the next 24 months (1).

were up about two percentage points in 2011 compared with 2010.

## Future of outsourcing

Many service vendors insist that outsourcing can improve organizational efficiency for their clients and that service providers can often offer better quality and more efficient services. And these services are not just for repetitive, low-value activities, or for testing, or fill–finish work. The 2011 study tends to confirm this claim in its measurement of trends in usage levels for the top 23 biopharmaceutical operations commonly outsourced. We asked respondents which activities they expected to outsource at "significantly higher levels" during the next 24 months. Surprisingly, the 2011 data show that upstream and downstream operations are going to be outsourced at a much higher rate than in previous years. The growth in other, less crucial operations were virtually flat. For example, the percentage of respondents indicating fill–finish activities would be outsourced at a higher rate, was 24.6% in 2011 compared with 24.8% in 2010.

Areas such as product testing and other assays continue to grow at double-digit rates. For example, nearly 20% of respondents indicated they would be outsourcing significantly higher levels of their product-characterization testing over the next 24 months. Tim Lee, deputy director of bulk manufacturing at Sanofi-Pasteur, notes, "The outsourcing of analytical test methods used in product characterization is a big trend as in-house testing labs become fully loaded with their manufacturing tests to release product. Also, many outsourced labs have specific expertise that industry doesn't have internally."

## Conclusion

The economic recovery has been slow, and uncertainty continues to restrain hiring, which means the pressure to outsource and offshore operations has yet to abate. The BioPlan study also indicates that many contract manufacturing organizations and service providers have been experiencing much greater pressures from their clients to keep costs in line, reduce nonessential services, and otherwise trim budgets. This pressure, in turn, has forced service suppliers to run leaner operations and curtail some of the value-added services that might have otherwise been provided. While the industry will continue to see growth among emerging contract biopmanufacturing providers in India and other Asia-Pacific locations, providers in the US and Western Europe will see more modest improvements.

The economic uncertainty also makes shorter-term contracts more popular, and clients are increasingly expecting work to be done on short-term cost-and performance milestones, rather than on long-term commitments and partnerships. The price cuts and shifts toward more transactional, short-term business is likely to damage long-term relationships and reduce the potential strategic value that outsourcing can bring to clients. As long as global economic uncertainty remains, outsourcing will continue to be used as a buffer for cost cutting, and hiring of costly operations staff may continue to be delayed. This change may, in the end, result in strategic shifts in how companies are valued if their core capabilities and institutional knowledge in manufacturing, process development, and R&D continue to be delegated to external providers.

## Reference

1. BioPlan Associates, Preliminary data from the *8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*, Publication for April 2011 (Rockville, MD), bioplanassociates.com/publications/bmcp.htm. **PT**

# A Unique Workflow for Linearity Testing using Automated Sample Preparation and UHPLC

## On Demand Webcast

Pharmaceutical Technology

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**ON DEMAND WEBCAST**

### Event Overview:

When validating a method according to the ICH guidelines, it is necessary to perform a linearity experiment. This requires the preparation of multiple calibration levels, analysis of the samples by liquid chromatography, and calculation/reporting of the results. Each of these steps can be very time consuming, and in many cases error prone. This is especially true if the analytical method being tested requires the measurement of multiple components.

In this webinar we will present a new way to tackle these challenges. The webinar will demonstrate an automated approach to sample preparation, the use of UHPLC to speed-up the analysis, and the use of advanced software tools for calculation and reporting of the results. When used in combination, these tools substantially shorten the linearity workflow, and significantly reduce error rate.

### Key Learning Objectives:

- Learn how automated sample preparation can save time and reduce error
- Learn how UHPLC can reduce sample analysis time by a factor of 5 or more
- Learn how a chromatography data system can fully automate calculation of the results

### Who Should Attend:

» Anyone who has to manually prepare samples and standards

» Anyone who works in pharma method development and QA/QC

» Anyone who wants to see how UHPLC can improve productivity in their lab

### Speakers:

**Joanne Ratcliff, PhD**
Marketing Project Manager
Mettler-Toledo

**Fraser McLeod**
Senior Director of
Product Marketing
Dionex Corporation

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METTLER TOLEDO

## Lubrizol Opens Application Center in Mumbai

Lubrizol opened an applications and business center in Mumbai to support its Advanced Materials business segment, which comprises pharmaceutical ingredients, personal care, engineered polymers, and coatings. The new facility is intended to strengthen Lubrizol's focus on polymers for controlled-release oral solid dosage forms, as well as to provide technology to generic-drug manufacturers in the region.

Located in the Jaswanti Landmark office complex, the new center houses a pharmaceutical laboratory equipped with tableting and granulating equipment, instruments for disintegration and dissolution testing, and instruments for granule or tablet characterization. The center will provide technical service and training to Lubrizol's clients. Lubrizol's regional technical centers in Mexico City, Mexico, and Brecksville, Ohio, also support the pharmaceutical ingredients market.

## Private-Equity Firm Acquires Confab

The portfolio company of RoundTable Healthcare Partners, an operating-oriented private-equity firm focused exclusively on the healthcare industry, acquired Confab Laboratories. Confab is a contract pharmaceutical manufacturer in St. Hubert, Canada.

Guy Lamarre, founder and former CEO of Confab, will remain active in the development of the business as vice-chairman of Renaissance., RoundTable's portfolio company. Nathalie Brisson was promoted to the position of president and general manager of Confab and assumed leadership of the daily business operations along with the other members of the management team.

## Catalent Executive Delivers Update on USP Guidance

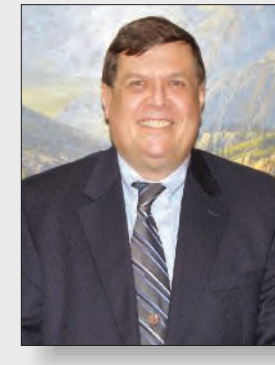
Mary Foster, vice-president of quality for Catalent Pharma Solutions and chair of the US Pharmacopeia (USP) Packaging, Storage, and Distribution Expert Committee, spoke about the latest update to the USP guidance on the packaging, distribution, and transportation of drug products at the 10th Annual Cool Chain Europe conference. Foster also described new *USP* General Chapters at the event, which took place on January 24–26 in Rotterdam, The Netherlands.

Foster provided an update about *USP* general chapter <1079>, including the final highlights of the document and the decision about what topics were included and excluded. She also described how companies can become involved in working on future USP guidance. Finally, Foster gave attendees information about new *USP* chapter work in areas such as anti-counterfeiting, ePedigree, and supply-chain best practices.

"It is important that the pharmaceutical and biotechnology industries, academia, regulatory agencies, and other interested parties understand how valued their input is to chapter revision and new-chapter writing for USP," said Foster in a Catalent press release. "We need experts from around the world to volunteer and help make a positive impact with this work."

## Q&A with

### Dan Klees, *business manager of life-science solutions at Magnetrol International*



**PharmTech:**
What is the biggest industry challenge you're now facing?

**Klees:**
Our customers have to manufacture more product of a better first-time quality at less cost. To accomplish this, energy use must be minimized, rework must be eliminated, the process must be optimized, equipment must be scheduled and used effectively, product hold times must be minimized, and compliance must be assured.

Our challenge is to help the customer to measure and optimize process parameters that affect costs while maintaining the safety, purity, and efficacy of their intermediate or drug. We need to be involved with our customers at the earliest stages of manufacturing design—preferably at the beginning of product development. Reliable, accurate process measurement and control solutions that optimize yield while minimizing cost have to be designed with the process, not after the process design.

**PharmTech:**
How do you stay abreast of new developments in the industry?

**Klees:**
We are actively involved with industry groups, such as the International Society for Pharmaceutical Engineering and the American Society of Mechanical Engineers's BioProcessing Equipment Committee, that develop the standards and practices for leading-edge facilities. Magnetrol also stays in close technical contact with its industry customers.

**PharmTech:**
Do you see a new industry trend emerging?

**Klees:**
One of the trends that we see is in the area of single-use processing systems. These systems do not require cleaning or steaming in place, which minimizes energy costs, chemical usage, and cleaning time. They also minimize the use of purified water, prevent batch-to-batch contamination, and allow for flexible manufacturing. Magnetrol is designing single-use instruments that will provide traditional functionality, accuracy, and reliability with the requirements of presterilization, low cost, and disposability.

## MANUFACTURING EQUIPMENT & SUPPLIES

### Tablet press

Specialty Measurement offers the MiniTab press, which is designed to manufacture tablets ranging from 0.5 to 4 mm in diameter. The introduction model can produce < 300,000 tablets/h; larger models will be capable of making > 2 million tablets/h. The compact size of the machine, less than 250 × 500 × 500 mm, makes it ideal for glove-box applications. **SMI,** *Lebanon, NJ • www.smitmc.com • tel. 908.534.1546*

### Dry-material feeder

The PureFeed AP-300 dry-material feeder was designed specifically for pharmaceutical processes. Users can disassemble the device quickly and easily. The machine includes a dual-arm agitation system for versatility in material handling. Its disposable and recyclable EPDM feed hopper complies with US Food and Drug Administration regulations. **Schenck AccuRate,** *Whitewater, WI • www.accuratefeeders.com • tel. 888.232.4828*

### Plunger-rod-inserting machine

The Hasta plunger-rod-inserting machine is available in speeds of 12,000 or 24,000 pieces/h. The unit has the flexibility to interface with upstream and downstream machines, can be customized for additional capabilities, and is pre-engineered to add a backstop-inserting unit to the syringe. **MG America,** *Fairfield, NJ • www.mgamerica.com • tel. 973.808.8185*

## MANUFACTURING EQUIPMENT & SUPPLIES

### Filter-integrity tester

Thirty years of design refinements have resulted in the Sartocheck 4 plus advanced filter-integrity tester. The unit incorporates productivity-enhancing features and is built to be durable. The device also was designed for the operator's ease of use. **Sartorius Stedim North America,** *Bohemia, NY • www.sartorius.com • tel. 631.254.4249*

### Tablet-compression accessories


Natoli's Tablet-Compression Accessories Catalog is a comprehensive catalog available to support the tablet-compression industry. The catalog is a resource that includes more than 150 pages of products, equipment, and references about setup, inspection, maintenance, and tablet analysis. All products listed in the catalog are available for worldwide shipment. **Natoli,** *St. Charles • MO, www.natoli.com • tel. 636.926.8900*

### Culturing set

SGM's DriAmp biological-indicator culturing set features Releasat medium and is designed for high-temperature, direct-air exposure or submersion in nonwater-based solutions. The DriAmp BI is a 1-mL, snap-top glass ampul containing inoculated silica. The Releasat medium provides a reduced incubation time of 72 h. A color change indicates positive test results. **SGM Biotech, Inc.,** *Bozeman, MT • www.sgmbiotech.com • tel. 406.585.9535*

## MANUFACTURING EQUIPMENT & SUPPLIES

### Pharmaceutical robot

The Stericlean robot automates processes in isolator and cleanroom environments. Designed to protect staff and products, the robot fully withstands decontamination with vapor hydrogen peroxide. Stäubli Robotics offers various solutions for aseptic automation. **Stäubli Robotics,** *Duncan, SC • www.staubli.com • tel. 800.257.8235*

### Validation and documentation

Fette Compacting America offers extensive validation and documentation specifically related to quality control, validation, and regulatory compliance. The company's documentation follows the Life-Cycle Design model and is admissible to FDA as validation documentation. Most documentation can be reformatted into customer-supplied document formats. **Fette Compacting America,** *Rockaway, NJ • www.fetteamerica.com • tel. 973.586.8722*

### Sanitary clamping

Continental Disc Corporation introduces the SANI-TORQ clamping device to tighten sanitary clamps to a specified torque setting. The new device tightens a standard 1-1/2"–4" (40–100 mm) sanitary clamp with a standard wrench until the proper torque value is reached. An audible click indicates the correct inch-pounds force has been achieved, and a self-limiting feature stops tightening the clamp. SANI-TORQ is left in place until the clamp is removed. **Continental Disc,** *Liberty, MO • pressure@contdisc.com • tel. 816.792.1500*

## MANUFACTURING EQUIPMENT & SUPPLIES

### Top-entering agitators

The PharMix Series 3000 and 4000 top-entering agitators are specifically designed for demanding pharmaceutical and biotechnology mixing applications. The units' robust shaft designs run in free air for cleaning in place and eliminate the need for stabilizing rings. Each agitator comes with a complete prevalidation documentation package. **DCI,** *St. Cloud, MN • www.dciinc.com • tel. 320.252.8200*

### Protein purification

The SciPure 200 single-use system is a purification platform designed to automate, document, and optimize protein purification. The system performs automated concentration and diafiltration and uses disposable fluid pathways. Its disposable tangential-flow filtration tube manifold incorporates temperature, pressure, and conductivity sensors. **SciLog,** *Middleton, WI • www.scilog.com • tel. 800.955.1993*

### Sterile disconnectors

Kleenpak sterile disconnectors from Pall Life Sciences are intended to enable users to disconnect sterile single-use systems in seconds. The products are easy to operate and validated to ensure that the disconnected systems remain closed and sterile, inside or outside a controlled-air environment. **Pall Life Sciences,** *Port Washington, NY • www.pall.com • tel. 800.521.1520*

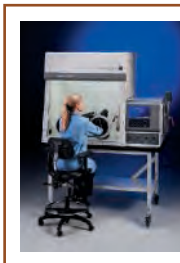
## MANUFACTURING EQUIPMENT & SUPPLIES

### Product catalog

Cole-Parmer's general catalog includes the latest fluid-handling, laboratory-research, industrial-process, and electrochemistry products. The catalog contains more than 2600 pages featuring brand names, such as Masterflex, Oakton, and Polystat. The catalog also includes information about Cole-Parmer's technical assistance, database tools, and calibration services. **Cole-Parmer,** *Vernon Hills, IL • www.coleparmer.com • tel. 800.323.4340*

### Diaphragm-valve actuator

Top Line's E360 diaphragm-valve actuator is designed to facilitate the maintenance of the actuator power unit. The actuator also enables users to change the functions of the unit without exposing the product process to atmosphere. The actuator is intended to eliminate product contamination, thus reducing product loss, delays, and costs. **Top Line Process Equipment,** *Lewis Run, PA • www.toplineonline.com • tel. 800.458.6095*



### Glove boxes

Labconco's Protector Filtered glove boxes are designed to offer all advantages of low-volume filtered ventilation enclosures and provide a totally isolated working environment. The products perform 99.99% efficient high-efficiency particle attentuation filtration and a leak-tight physical barrier to protect the operator from exposure to potentially hazardous materials. **Labconco,** *Kansas City, MO • www.labconco.com • tel. 800.732.0031*

## MANUFACTURING EQUIPMENT & SUPPLIES

### Cleaning system

I Holland's Ultrasonic System automatically cleans, rinses, dries, and lubricates as many as 240 punches and dies in a 30–40-min cycle. The system is available in an ultrasonic frequency of 25 kHz for coarse and preliminary cleaning, and of 45 kHz for fine cleaning. **I Holland,** *Cape Coral, FL • www.iholland.co.uk • tel. 732.310.4433*

### High-capacity capsule filter

Meissner's UltraCap H.D. single-use, high-capacity capsule filter is available in a 50-in. (127-cm) configuration for large-volume filtration. The capsule filter is optimized for continuous and batch processing in biomanufacturing operations and for pre- and final filtration in pharmaceutical applications. The product can be specified with removal ratings from 0.04 to 99 µm. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

### Current switches

The Series CCS current switches from Dwyer are suitable for monitoring the operating status of fans, pumps, and motors. The self-powered switches can be hung or tied directly to cables or wires. Split-core models can be installed without disconnecting the cables of existing installations. Light-emitting diodes confirm that the current is flowing through the core. **Dwyer Instruments,** *Michigan City, IN • www.dwyer-inst.com • tel. 800.872.9141*

## OUTSOURCING & CONSULTING SERVICES

### Drug-delivery solutions

For more than 50 years, companies have looked to 3M Drug Delivery Systems for solutions to help their products meet the market's needs. 3M offers inhalation and transdermal drug-delivery systems and components, including dry-powder inhaler and microneedle technologies, plus state-of-the-art contract manufacturing services to help ensure technical success. **3M Drug Delivery Systems,** *St. Paul, MN • www.3m.com • tel. 800.643.8086*


### Contract manufacturing

A brochure from Ben Venue Laboratories describes the company's contract manufacturing services. Capabilities include the development and production of dosage forms such as sterile suspension, emulsion, liposome, microsphere, lyophilized, and liquid injectables in aqueous or nonaqueous solvent systems. The company produces batch sizes from clinical to commercial scale. **Ben Venue Laboratories,** *Bedford, OH • www.benvenue.com • tel. 440.232.3320*


### Development service

Dow's Feasibility Assessment for dermatological product development helps clients make a decision about whether to pursue potential topical drug candidates. The service includes an evaluation of candidates' physiochemical properties as they relate to penetration. The service also encompasses solubility and stability studies in solution, *in vitro* skin irritation, and *in vitro* skin penetration testing. **Dow Pharmaceutical Sciences,** *Petaluma, CA • www.dowpharmsci.com • tel. 707.793.2600*

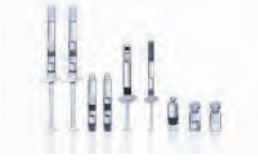
## OUTSOURCING & CONSULTING SERVICES

### Contract services

Patheon is a leading provider of contract development and manufacturing services to the global pharmaceutical industry. The company supplies products and services to approximately 300 of the world's leading pharmaceutical and biotechnical companies. Patheon's fully integrated worldwide network helps ensures that customer products can be launched anywhere in the world. **Patheon,** *Research Triangle Park, NC • www.patheon.com • tel. 905.821.4001*

### Job-focused training

PDA's Training and Research Institute provides intensive, job-focused training that clients can apply immediately. The curriculum is designed to foster professional development in areas such as aseptic processing, biotechnology, environmental monitoring, filtration, microbiology, quality, regulatory affairs, training, and validation. Courses can be customized and provided at the client's location. **Parenteral Drug Association,** *Bethesda, MD • www.pda.org • tel. 301.656.5900*



### Drug-delivery systems

Vetter offers a portfolio of drug-delivery systems. Its commercial manufacturing division aseptically fills syringes, cartridges, and vials according to high quality and safety standards. The company also offers patient-friendly injection systems, such as the Vetter Lyo-Ject dual-chamber syringe and the dual-chamber cartridge V-LK. **Vetter Pharma International,** *Ravensburg, Germany • www.vetter-pharma.com • tel. +49 751 3700*

## OUTSOURCING & CONSULTING SERVICES

### Controlled packaging environment

Ropack, a leader in innovative packaging for the pharmaceutical and nutraceutical industries, provides a controlled production environment for blister, cold-form, and stick packaging. The Class 100,000 dedicated manufacturing suites deliver low relative humidity (approximately 20%) and low residual oxygen (< 2%) in a temperature-controlled environment. **Ropack,** *Montréal, Canada • www.ropack.com • tel. 888.353.7090*

### Contract testing laboratory

Impact Analytical is a contract testing laboratory that works with more than 300 companies around the world. The company strives to provide high-quality analytical service to the pharmaceutical, medical device, packaging, and specialty-chemical industries. The company is registered with the US Food and Drug Administration and complies with good manufacturing practice. **Impact Analytical,** *Midland, MI • www.impactanalytical.com • tel. 989.832.5555*

## CLEANROOM EQUIPMENT & SUPPLIES

### Cleanroom pass-through chambers

Terra's BioSafe pass-through chambers incorporate coved corners and ultra-smooth 304 or 316 stainless-steel surfaces to simplify cleaning and sterilization in aseptic applications. No-lip edges eliminate clearance obstructions and facilitate material transfer. A rugged mechanical interlock, mounted outside of the pass-through chamber, prevents cross-contamination. **Terra Universal,** *Fullerton, CA • www.terrauniversal.com • tel. 714.578.6000*

## CLEANROOM EQUIPMENT & SUPPLIES

### Sterile wipes

Veltek offers sodium-hypochlorite and hydrogen-peroxide wipes that are Class 10 laundered, filtered at 0.2 μm, and formulated with *US Pharmacopeia* water-for-injection. The products have laser-cut edges and are guaranteed sterile with lot-specific documentation. **Veltek,** *Malvern, PA • www.sterile.com • tel. 610.644.8335*

## PACKAGING EQUIPMENT & SUPPLIES

### Transfer packaging for prefillable syringes

BD TSCF packaging ensures the secure transfer of sterile prefillable syringe components into the pharmaceutical filling environment. The packaging is compatible with IDC Biosafe doors for aseptic filling machines within isolator or barrier systems. This packaging is part of the BD SCF global offer, which features expertise in sterile processing of preservative-free drugs; secure, reliable, easy-to-use systems; and drug master files and technical dossiers. **BD Medical–Pharmaceutical Systems,** *Franklin Lakes, NJ • www.bdpharma.com • tel. 800.225.3310*


### Packaging solution

The NextBottle package from Catalent and One World Design and Manufacturing Group is designed to improve patient compliance. The product's dial mechanism dispenses one pill at a time and automatically reminds patients of the last day that a pill was taken. **Catalent Pharma Solutions,** *Somerset, NJ • www.catalent.com • tel. 866.720.3148*

## LABORATORY EQUIPMENT & SUPPLIES


### Near-infrared analyzer

The MB3600-PH Fourier transform-near infrared analyzer was designed for quality assurance, quality control, research, and at-line process analytical technologies applications. The instrument is maintenance-free and features a user-friendly software interface that enables operations that comply with 21 *CFR* Part 11. It analyzes solid and liquid samples nondestructively. **ABB,** *Québec, Canada • www.abb.com • tel. 418.877.2944*

### Visual-observation tool

The APK visual-observation tool is suitable for random-sampling manual inspection. Users can program spin speed according to liquid viscosity or container diameter, thus providing repeatable rotation speed and duration for inspected containers. The APK allows the human eye to detect foreign particles easily. **Eisai Machinery USA,** *Allendale, NJ • www.eisaiusa.com • tel. 201.746.2111*

### Process-analysis system

The ProFoss process-analysis system is based on high-resolution diode-array technology. It provides nondestructive analysis of pharmaceutical and chemical products directly in the process line without bypass. The solution helps to optimize the use of raw materials and to consistently run production closer to target specifications. **FOSS NIRSystems,** *Laurel, MD • www.foss-nirsystems.com • tel. 301.680.9600*

## LABORATORY EQUIPMENT & SUPPLIES

### On-line TOC analysis

To help pharmaceutical companies improve quality and reduce costs, GE Analytical Instruments offers a science- and risk-based program for achieving real-time release of pharmaceutical water. The program streamlines a complex process and helps companies move total organic carbon testing from the laboratory to the production floor in approximately six months. **GE Analytical Instruments,** *Boulder, CO • www.geinstruments.com • tel. 800.255.6964*

### Benchtop incubators

Caron introduced two benchtop carbon-dioxide incubators that incorporate the company's GelJacket active gel insulation technology. The technology is incorporated inside every wall of the incubator chamber and is designed to retain more heat than other insulation technology available in incubators. The GelJacket carbon-dioxide incubators fit on a benchtop and take up minimal laboratory space. **Caron Products and Services,** *Marietta, OH • www.caronproducts.com • tel. 800.648.3042*


### Chromatography products catalog

Restek's 2011 "Chromatography Products" catalog celebrates the company's 25th anniversary with 800 pages of chromatography products. The catalog includes columns, replacement parts, tools, and accessories for gas and high-performance liquid chromatography. **Restek Chromatography Products,** *Bellefonte, PA • www.restek.com • tel. 814.353.1300*

### CLEAN ROOM SUPPLIES



### EQUIPMENT & SUPPLIES



### CONTRACT MANUFACTURING



### MANUFACTURING/PROCESSING EQUIPMENT

*MANUFACTURING*



*MANUFACTURING*



*OUTSOURCING RESOURCES*

## CENTRIFUGES



## CHEMICALS/EXCIPIENTS/API'S

### Bulk Oils



## LAB EQUIPMENT

### Airflow Diagnostic Tools



## MANUFACTURING/PROCESSING EQUIPMENT

### Mixing/Blending/Drying



## MANUFACTURING/PROCESSING EQUIPMENT

### Used



## OUTSOURCING RESOURCES

### Analytical Testing



## RECRUITMENT

*contin. from page 98*

FY2011 budget provides $2.5 billion in budget authority and $4 billion in total program resources for FDA in this regard. The funds include efforts to bring more safe, effective, and low-cost generic drugs (including follow-on biologics) to the US market (9). These activities will ultimately help to make safe drugs more affordable and readily available to American consumers.

## Potential remedies

But in the immediate future, reimportation remains a controversial issue. Making reimportation legal may not bring long-term benefits to the US market because of already mentioned concerns over safety. Reimportation also could reduce companies' revenue and thereby deplete funding for new-drug research and development.

American consumers will benefit most when drug prices are controlled at a global level. The authors propose the formation of an international body of pharmaceutical leaders to monitor the flow of pharmaceuticals across borders and to regulate prices internationally. (FDA and other regulatory agencies do not regulate prices.) An international consortium of pharmaceutical companies could work to find common ground with consumers on drug pricing internationally, which could reduce drug reimportation.

An active dialogue between company representatives and government representing American consumers also is necessary to keep drug reimportation off the table. Educating consumers about the risks of bringing drugs into the country illegaly is crucial, as is discussing alternatives to low-cost products.

## References


1. T.S. Rector and P.J. Venus, *Health Aff.* **23** (2004) 213–222.
2. D.G. Safran et al., *Health Aff.* Supp. web exclusive (2002), pp. W253–68.
3. Public Law 108-173, Medicare Prescription Drug, Improvement, and Modernization Act of 2003.
4. HHS, Medicare Modernization Act Update–Overview, www.cms.gov/PrescriptionDrugCovGenIn/01_Overview.asp, accessed Jan. 5, 2011.
5. HHS, Report on Prescription Drug Importation (December 2004), http://archive.hhs.gov/importtaskforce/Report1220.pdf, accessed Dec. 1, 2010.
6. American Progress, "Prescription Drug Reimportation: The Law and Its Problems," www.americanprogress.org/kf/bgreimp.pdf, accessed Dec. 1, 2010.
7. US Congress, H.R. 1298: *Pharmaceutical Market Access and Drug Safety Act of 2009*, www.govtrack.us/congress/bill.xpd?bill=h111-1298, accessed Jan. 5, 2011.
8. HHS, FY2010 Budget in Brief, http://dhhs.gov/asfr/ob/docbudget/2010budgetinbrief.pdf, accessed Dec. 20 2010.
9. HHS, FY2010 Budget, www.gpoaccess.gov/usbudget/fy11/pdf/budget/health.pdf, accessed Dec. 20, 2010. **PT**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# Ad Index

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# Friend or Foe: Prescription Drug Reimportation in the US

**Om V. Singh and Thomas E. Colonna**

## Congressional actions have hampered cross-border drug importation and limited choice.

Innovation in medicine offers great hope for improving lives, and pharmaceutical research companies are making every possible effort to fight life-threatening diseases to ensure people's health. Unfortunately, consumers do not always have affordable access to prescription drugs that can help treat their medical conditions.

In the United States, 15 to 25% of the population has reported not filling a prescription on time and/or reducing a prescribed dosage due to cost (1, 2). Although the US Medicare Prescription Drug, Improvement, and Modernization Act (MMA), enacted in 2003, provided the largest overhaul to date of America's public health program, many beneficiaries still face challenges in getting healthcare and medication benefits (3, 4). And while the Affordable Care Act of 2010 increased benefits and access for Medicare beneficiaries, many of the legislation's overhauls have yet to be implemented.

As a result, many Americans continue to purchase drugs outside US borders at a lesser cost. Many of the drugs bought abroad were actually approved by FDA, manufactured in the US, and sold to other countries. Canada, in particular, is a prime recipient of such products. When these drugs are sold to Americans who bring them back into the US, they become illegally imported and hence are referred to as "reimported drugs."

Brand-name drugs that are manufactured in foreign countries, on the other hand, can be legally imported into the US if they comply with the Food, Drug, and Cosmetic Act (FD&C Act). This process is often referred to as "drug importation." Under the FD&C Act, any entity that intends to import prescription drugs into the US must ensure that the drug products are FDA-approved, meet all US manufacturing and labeling requirements, and do not violate the FD&C Act's import and and export section (5).

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Although there is always some concern about the safety and quality of imported drugs, reimported drugs, in particular, carry more potential for being illegitimate and unsafe. Specifically, they may lack proper authentication, originate from unreliable outlets, be expired or contaminated, and lack correct dose information or directions for use. FDA has traced multiple violations of drug reimportation laws and found that most reimported drugs do not include the required label information.

Nevertheless, for many US residents, financial concerns outweigh the risks of prescription drug reimportation. There is a need, therefore, to prevent consumers from falling prey to online marketing of unsafe drugs.

### Congressional activity

In 2000, the US Congress passed the Medicine Equity and Drug Safety (MEDS) Act to provide Americans with a legal means to obtain low-cost prescription drugs from industrialized countries. Later, MMA sought to prevent Americans from seeking less expensive drugs from Canada by authorizing drug reimportation, but providing veto authority to the US Secretary of Health and Human Services over its implementation, and to date, the secretary has used this veto power (6). Thus, MMA has not enabled safe drug reimportation.

In 2009, US Senator Byron Dorgan (D-ND) pushed to include drug importation in President Obama's healthcare reform bill. Dorgan's legislation, called the Pharmaceutical Market Access and Drug Safety Act of 2009 (PMADS), was designed to establish a system for American consumers to import low-cost prescription drugs safely (7). The PMADS Act was designed to legalize reimportation as well. The amendment is still in legislative process.

The President's Fiscal Year 2010 budget request included $5 million to allow FDA to begin working with various stakeholders to develop policy options related to drug importation (8). The

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