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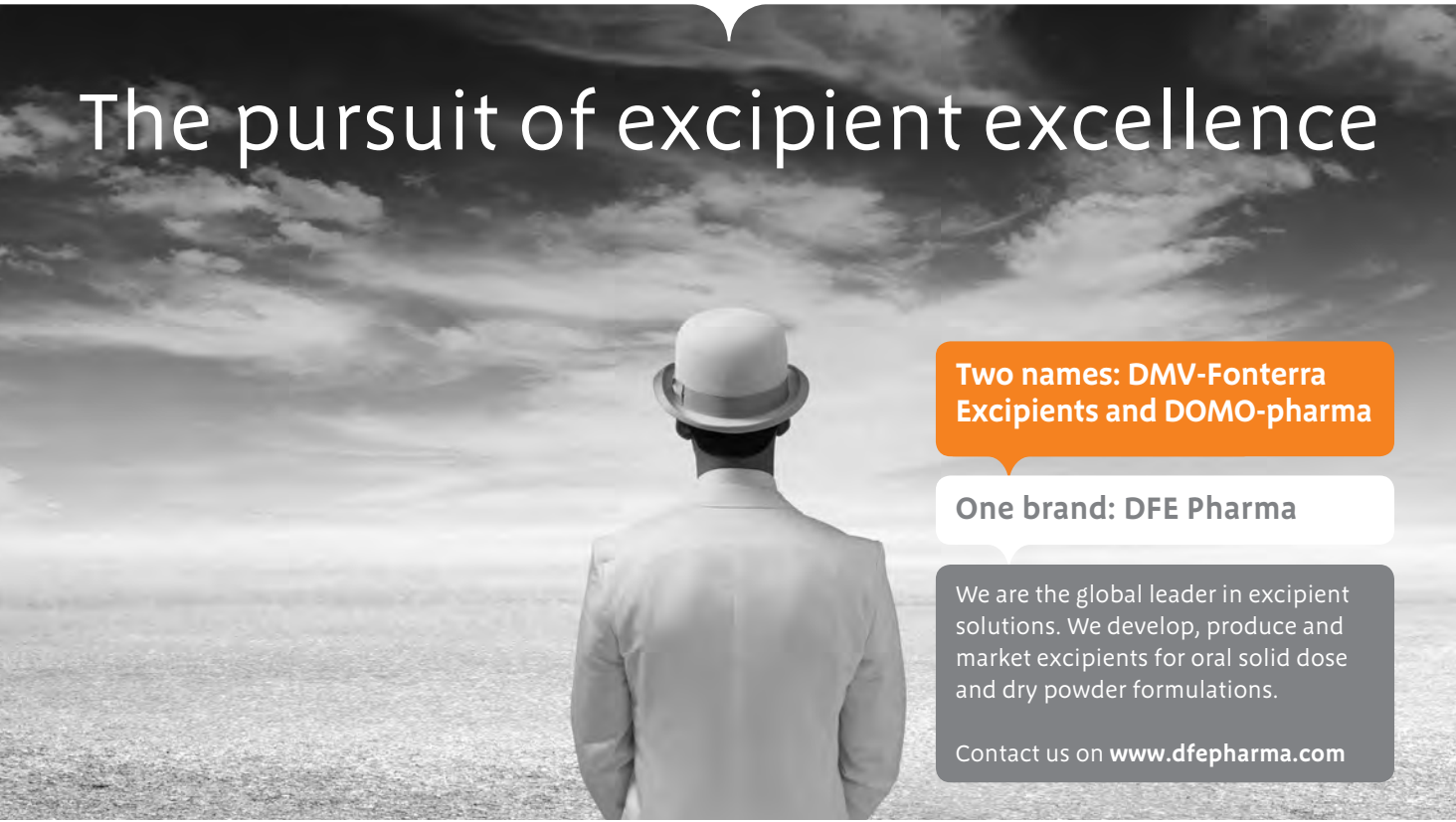

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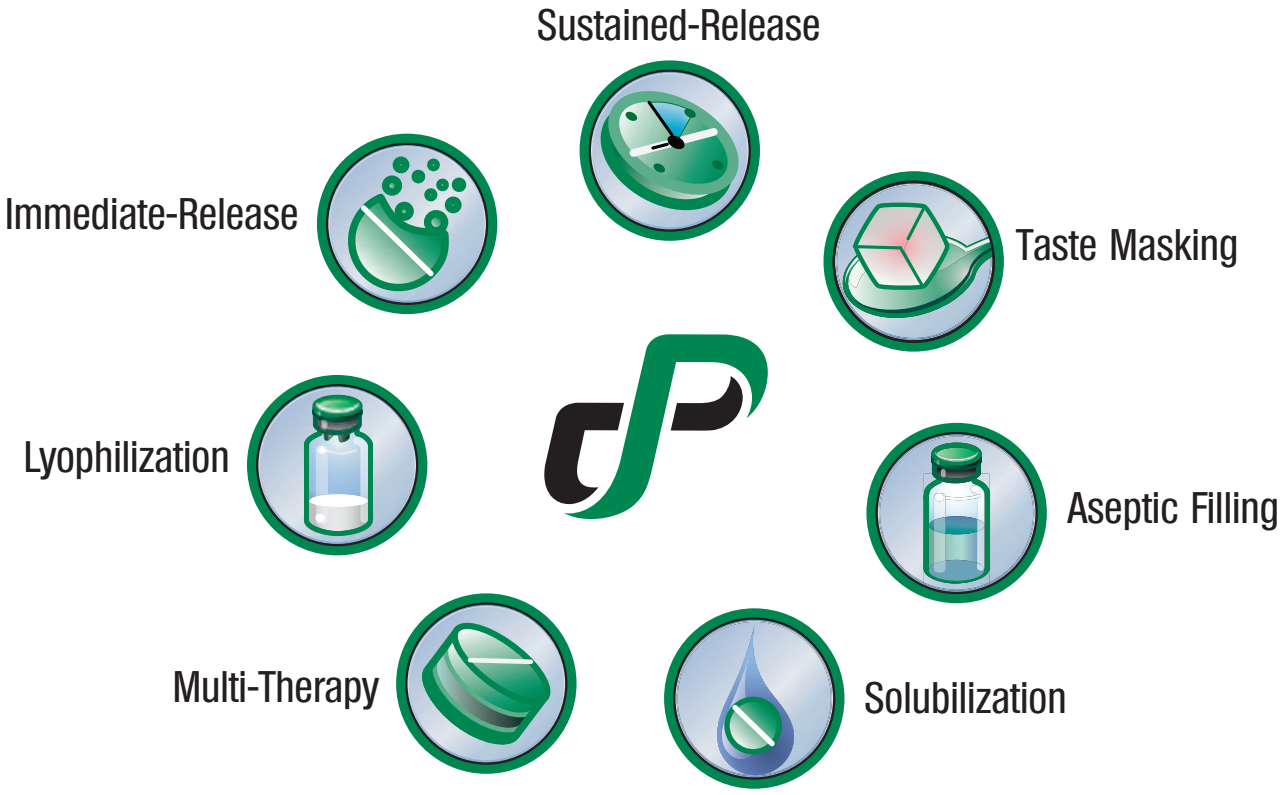

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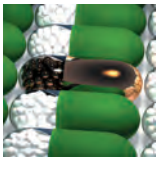

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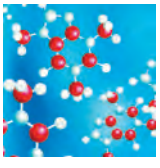

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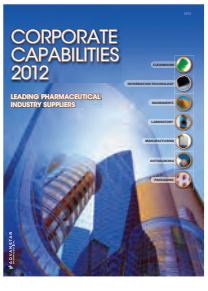

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PHARMACEUTICAL TECHNOLOGY (Print ISSN: 1543-2521, Digital ISSN: 2150-7376) is published monthly, except two issues in June, by Advanstar Communications, Inc., 131 W. First St., Duluth MN 55802-2065. **Subscription rates:** US and possessions — 1 year (13 issues), $70; 2 years (26 issues), $125. Canada and Mexico — 1 year, $95; 2 years, $145. All other countries 1 year, $135; 2 years, $250. International price includes air-expedited service. Single-copies (prepaid only) — US, $8; outside the US, $10. Back issues (if available): US and possessions — $21; all other countries — $25. Include an additional $6.50 per order plus $2 per additional copy for US postage and handling. If shipping outside the US, include an additional $10 per order plus $3 per additional copy. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to *Pharmaceutical Technology*, PO Box 6188, Duluth, MN 55806-6188. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: Pitney Bowes, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A.

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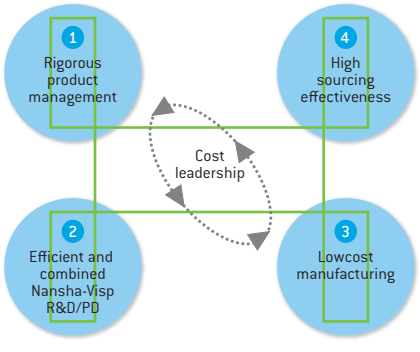

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When Disaster Strikes at Home

Angie Drakulich

Keeping tabs on crucial medicines should be part of consumers' and manufacturers' crisis plans.

The editorial offices of *Pharmaceutical Technology* are based in New Jersey, so when Hurricane Sandy hit last month, we were all affected. Flooding and high winds destroyed many coastline homes along with well-known destinations across Atlantic City, the Jersey Shore, and the neighboring Manhattan boroughs. Suburban communities and businesses (including many US biopharma manufacturing headquarters) across the state were without power for days and schools were shutdown for a week or more in several counties. President Obama declared the state, along with New York, a major disaster area. The entire ordeal was quite surreal, and our team considers ourselves to be lucky that we made it through unscathed. Our thoughts go to those still recovering from the storm and trying to get back to normal.

Many common questions arose during the hurricane and its aftermath, including how long food products could be considered safe to eat without refrigeration and where the closest open gas station was to refill generators. Pertaining to our industry were questions about medications that required refrigeration (primarily injectables and liquids), prescriptions that needed refilling (many doctors' offices and drugstores were closed due to flooding and power outages), and drug products that had gotten wet or been lost in the storm.

Angie Drakulich is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to adrakulich@advanstar.com.

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Fortunately, FDA has a consumer webpage devoted to drug safety after a natural disaster, whether it be exposure to fire, unsafe water (key for drugs that have to be reconstituted), or lack of refrigeration. Certain life-saving drugs (e.g., insulin) can be used even if not cold as long as they are not past their expiration date, says the agency webpage. There is also FDA information on medical devices and their safety during a crisis, and even an agency guidance aimed at sales representatives on how to deal with lost or stolen drug samples in the aftermath of a disaster (looting in general was quite prevalent after Hurricane Sandy).

There should be more emegency information on drug-product labels.

There are also some rules of thumb to follow in any emergency-preparedness plan. Many patient advocates recommend having on hand a 30-day supply of regularly used medicines (both prescription and over the counter), as well as extra quantities of devices needed to administer medications. But as a consumer, it seems there should be even more information available for those unfortunate times when something out of human control affects the medications we need. As an asthmatic, for example, I was concerned about my inhaler's pending expiration date and not being able to get a refill without having to go the emergency room, which by the way, would have been impossible given that the end of my street had a 60-foot tree and power lines lying across it.

I recognize that drug labels are already quite lengthy, but it may be worthwhile to add a few more details. For instance, language may focus on how long a cold-chain medicine can go without refrigeration, or how long a drug exposed to excessive heat can be considered safe, or the reasons behind drug-product expiration dates. Some of these details may be in medication guides that come with drug products, but even those of us in the pharma industry know that the majority of end users do not read those packets in full or keep them. This is probably an area where FDA and pharmacists can do a better job educating consumers about the importance of medication guides.

Another piece of information worth including on labels may be where to find information during emergency situations. As so many discovered during Hurricane Sandy, we rely heavily on technology to get our information. Smart phones, in particular, became indisposable in the aftermath of the storm when power outages held hostage traditional television, phone, and Internet access. Pharma companies could consider, for example, having active Twitter feeds during emergencies so that people can still access crucial information.

Various disasters and crises are bound to affect the global community in the future. Now is the time to think about the crucial information we will need to have on hand—and attached to our medications—when that next disaster strikes. **PT**

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Mice on a Mission

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

To ensure the accuracy of scientific testing, protect the subjects to avoid data contamination.

Party animals

"My first job out of college was at a pharmaceutical toxicology animal facility," our GMP Agent-In-Place reminisced. "The purebred white mice under study were kept, separated by sexes, in the standard plastic tray cages. A few months into the study, some mice were pregnant, and the babies were brownish. This indicated that the male was a wild animal that somehow got into and out of the cages. We wondered if it was still wandering around in our facility," our Agent laughed. "We had to discard the data from those particular cages to be sure the pregnancies weren't affecting our results."

Sterile or not?

"We performed product bulk-sterility tests by sampling the product through the filling tubing," explained our GMP Agent-In-Place. "When we had several failing bulk-sterility tests in a row, we were worried. Our investigation uncovered that the failures were artifacts caused by sampling and sample handling errors, but such errors are nearly impossible to prove. Our main evidence showed that repeated tests passed in each case. This was not a patient safety issue as we sterile-filtered the bulks for a second time before filling as allowed by our license. However, there was a problem with the process for taking sterile bulk samples if the process is causing failures. We identified aseptic sampling ports that could be added to the sterile bulk vessels at a cost of $8000 each to correct the failure. With 12 vessels, however, the cost was more than we had available in the budget for the fiscal year, and no one wanted to approach headquarters for the money. We did add the sampling ports the next fiscal year."

Our investigation uncovered that the failures were artifacts caused by sampling and sample handling errors, but such errors are nearly impossible to prove.

Calculating inspector

"We use alcohol in our manufacturing process," stated our GMP Agent-In-Place. "So the local Bureau of Alcohol, Tobacco, and Firearms inspector came to visit to verify our submissions as to usage. In our records we calculated purchasing, storage, and usage in liters. However, all of the inspector's formulas were in gallons and he needed a conversion. Even though I explained how it was done, he seemed to not be able to manage the conversion. I did the calculations for him, and gave him a complete, detailed sheet showing the numbers, the formulas, and the conversion factors used. Then he sat down at an empty desk, opening his briefcase and pulled out a tape dispenser, a stapler, and wrote out the entire report by hand."

Rotating employees

"I was asked to help interview new staff by a colleague in the global quality department," began our GMP Agent-In-Place. "He wanted a second opinion to assist with the evaluation process, and thought my 30 years in the industry would help him. When we sat down at the end of one particular interview, I voiced concern that the candidate changed jobs every two years, and this wouldn't allow him to be very effective for us as it takes six months or more to learn a new company and their processes. My colleague was indignant, stating that was his resume pattern as well."

"I had to laugh to myself," our Agent went on. "When I helped interview him for his position, that was my concern then as well. It turned out he left the company after only three years. I don't need to change jobs every two years. On average, I've had a new boss every two years within the same company."

Thank you

This is my last column. I have enjoyed the opportunity to write and hope you have found Agent-In-Place both entertaining and educational. Thank you.

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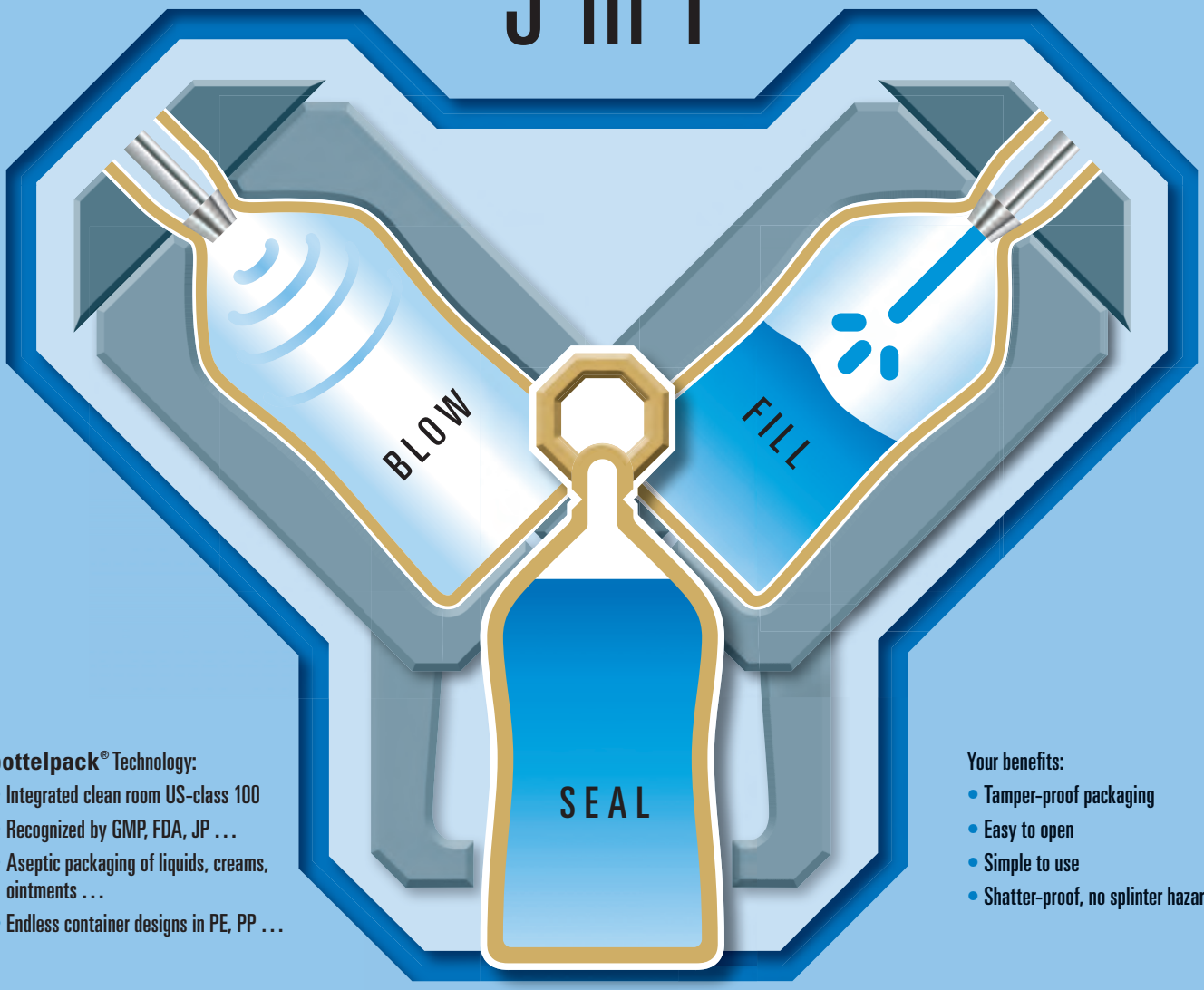

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In the Field

Report from: South Korea

Jane Wan

Domestic companies are changing their business models in response to recent drug price cuts.

Four domestic companies filed a suit against the Ministry of Health and Welfare of South Korea claiming that the recent price cuts made by the ministry have affected their businesses. On April 1, 2012, drug prices were reduced by an average 17% and cuts affected the prices of 6506 drugs across the board. The first cut, announced in 2011, decreases the price of off-patented drugs 30%, with the price of the first generic drug set at 60% of the price of the off-patented drug. Originally, prices of off-patented drugs decrease by 20%, while the first generic version is set at 68% of the off-patented drug. The second cut reduces the price of drugs due to illegal rebates. The combination of the two cuts means that certain drugs will undergo double-price reduction and the final price rate can be up to 53.55%.

Pharmaceutical companies are crying foul because these cuts would have a direct impact on their business profits even though the agency claimed that this move would ensure market sustainability and eradicate the problem of illicit rebates. In fact, a Sinhan Investment & Securities source has indicated that the majority of companies experienced a 20% fall in profits since the policy took effect.

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KEVIN FOREST/THINKSTOCK

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In response to their declining fortunes, some companies have opted to increase prices of their over-the-counter (OTC) drugs while others have boosted their R&D expenditure. Domestic companies such as Dong-A Pharmaceutical and LG Life Sciences have committed 22% and 19%, of net sales on R&D, respectively.

Cher Boon Piang, an analyst for Asia Pacific Pharmaceutical and Healthcare of Business Monitor International (Asia), says, "Given the price cuts, companies may withdraw drugs that are not profitable. Local companies may even move away from generics. There is also a shift towards biosmiliars that opens opportunity for companies." In October 2011, Dong-A Pharmaceutical joined hands with Tokyo-based Meiji Seika Pharma to build a biosimiliar plant in Songdo. Recently, local companies Yuhan Corp and Teregen ETEX are collaborating to commercialize the provision of individual genome services.

The recent US-Korea free-trade agreement (FTA) has also crippled domestic players as it contains provisions protecting the intellectual property rights of original drug developers. For instance, the Korean agency has to inform original manufacturers if there are companies looking to produce generic versions. Companies are denied market approval if an objection is posed by original drug manufacturers and when the claimed patent exists. It is also mandatory for the generic manufacturer to provide safety and efficacy information to ensure that the generic version does not infringe on the original one.

Perhaps a gradual price cut would have helped in alleviating pressures faced by industry players in South Korea. Cher says, "In general, companies face[d] both financial and time issues when two price cuts were introduced in 2011. If price reduction is gradual and made known to companies in a timeframe that prepares them for such reduction, these companies can draft and implement strategies to minimize the impact of price reduction. Moreover, it is easier to have short-term solutions against gradual price cuts compared to a larger one-off reduction."

Cher points out that price cuts cannot be the only solution to contain rising government expenditures and it is also unfair to shift the burden onto companies. Instead, the government should look into ways to cut expenditure by subsidizing only the necessary and/or increase premiums. These strategies may create a negative impression, but they are essential if a country is not doing well economically. In addition, the burden of healthcare costs should rest on individuals instead, he adds.

Clearly, the objectives of the government and the pharmaceutical industry players differ greatly. On one hand, the government seeks to lower healthcare costs. On the other hand, industry players are looking for ways to maximize profits. Asked if a balance can be struck between both parties, Cher says, "The level of compromise is dependent on the attractiveness of the market. Typically, an attractive market allows the government to push through its policies as companies are willing to forgo higher profit margins in exchange for sustainable growth over a time period."

Price cuts cannot be the only solution to contain rising government expenditures and it is also unfair to shift the burden onto companies.

The South Korean market is characterized by its aging population and an affluent population. Growth potential is limited as it has evolved to a developed market, and industry players expect it to have established regulations. Therefore, it makes sense that industry players are pre-alerted of any policies in the government's agenda. For example, industry players were informed in 2010 of the price disclosure policy to take effect in 2012. In Japan, industry players understand that it is the usual practice that price cuts occur once every two years.

Despite its fragmented market and the price-cut setback, South Korea is ranked among the world's top 12 with $8 billion annual sales. Cher adds, "In the long run, it has the necessary ingredients to continue with its successful pharmaceutical industry, strong support for innovation, the willingness of the private sector to explore these innovative technologies and the demographic profile also supports increased drug usage. The conflict between the government and industry will definitely arise again in the future, but we believe the two parties will reach a compromise. "

—Jane Wan is a freelance writer based in Singapore

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Informex's 2013 annual meeting, The Global Chemical Marketplace, is being held on Feb. 19–22 in Anaheim, California, at the Anaheim Convention Center. The exhibition and conference program will feature more than 500 exhibitors and 4000 attendees.

The annual meeting will provide attendees with a look at the global fine, specialty, and custom chemical market, targeting members of the pharmaceutical industry and the biopharmaceutical sector as well as the cosmetics/personal care industry, agrochemical manufacturing industry, and the plastics/polymers industry.

In addition to a full range of exhibitors, Informex has a complete educational conference planned that will focus on topics in the areas of specialty chemicals, including the latest information on contract manufacturing, petrochemicals, and agrochemicals; contract manufacturing in the pharmaceutical industry; regulatory compliance; and new chemical trends. More information can be found online at www.informex.com.

Join our online community

- **Have you checked out the PharmTech Group on LinkedIn? Active discussions are happening by the hour.**
- **PharmTech Talk, our daily editorial blog, covers the latest news and conference beats, at blog.PharmTech.com.**
- **Finally, don't miss the Twitter@PharmTechGroup feed for industry insights and news leads.**

Zone in on: Gene Therapy

Europe's First Gene Therapy Approved

The European Commission (EC) has issued final approval for Europe's first gene therapy—a treatment for a rare genetic disorder that currently has no other treatment options. According to a press statement, the treatment is the first gene therapy to be approved by regulatory authorities in the Western world.

uniQure's Glybera (alipogene tiparvovec) is intended for patients with lipoprotein lipase deficiency (LPLD) suffering from recurring acute pancreatitis. LPLD is an inherited disorder affecting approximately one or two people per million. Patients are unable to metabolize fat particles in the blood, leading to inflammation of the pancreas and, in some cases, early onset of diabetes and cardiovascular complications. Using adeno-associated virus vectors as a delivery vehicle, Glybera adds working copies of the lipoprotein lipase gene into muscle cells to enable enzyme production.

"The final approval of Glybera from the EC marks a major step forward in making gene therapies available not only for LPLD but also for a large number of rare disease with a very high unmet medical need," Jörn Aldag, CEO of uniQure, said in a statement. The company is planning to also apply for regulatory approval in the US, Canada, and other markets.

The European Medicines Agency (EMA) first recommended Glybera for approval in July 2012, with the EMA's Committee for Medicinal Products for Human Use (CHMP) recommending the granting of a marketing authorization under "exceptional circumstances." uniQure first submitted Glybera as a treatment for LPLD to the EMA in 2009, but received a negative opinion. However, in early 2012, the EC asked the EMA to re-evaluate the application in a restricted group of patients with severe or multiple pancreatitis attacks. Commercial rollout of the treatment is expected to begin in the second half of 2013.

—Stephanie Sutton

PharmTech's Bookshelves Over the Years

As *PharmTech* wraps up its 35th anniversary year, we asked readers and editorial advisory board members how many back issues of the magazine they have on their bookshelves. Being able to refer back to previously published peer-reviewed articles, special reports, and favorite columnists' analyses makes holding onto past volumes worthwhile. On the left is a picture of board member Lynn D. Torbeck and his personal *Pharmaceutical Technology* library. Think you have even more back issues? Send a picture to shaigney@advanstar.com and we may include it in a future issue.

Editors' Picks of Pharmaceutical Science & Technology Innovations

THE LATEST IN MANUFACTURING AND EQUIPMENT

Fluid-bed system provides optimized granulation and drying

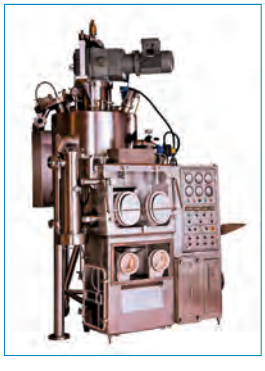
L.B. Bohle has extended its range of fluid bed systems with the introduction of the BFS 240. The system is equipped with eight tangential spray nozzles, that have been designed for direct injection to the product bed near the distributor bottom. This positioning prevents caking at the spray head and enables homogenous and fine spraying of the product. Dust-free suction and discharge of the product bowl is performed through the use of a patented, multifunctional valve directly above the distributor bottom. In addition, the design features a low number of gaskets, valves, and vents, which makes cleaning easier. The working volume of the system is up to 480 L, which is equivalent to a batch size of approximately 240 kg.

L.B. Bohle Maschinen + Verfahren GmbH
www.lbbohle.de/en
Systems are available worldwide

Capsule filler with multiple dosing units is designed for small runs

MG America's FlexaLAB capsule filler, which can produce up to 3000 capsules per hour, is designed for research and development, clinical trials, and small-batch production. The FlexaLAB can function with either continuous or intermittent motion. Installing multiple dosing units allows the FlexaLAB to manufacture capsules with combinations of products. The machine can fill powders, pellets, microtablets, tablets, liquids, and certain low-dosage powder inhalants and can perform capsule-into-capsule functions. The machine includes a touch-screen panel and PLC for machine-functions control. Machine speed can be adjusted from the monitor.

MG America
www.mgamerica.com
Capsule fillers are available in the US, Canada, and Puerto Rico



Filter dryer agitator aids production processes

API manufacturers can perform efficient cake drying during filtration and separation processes with PSL's agitated nutsche filter dryers. The systems feature a series of sharp curved blades with spaces at different specific points of each arm. When being moved and lifted between the gaps within the filter dryer agitator, the product moves at a lower velocity and is swept by the second arm of the blade to achieve efficient mixing at different velocities. The curved blades can also penetrate difficult cakes without undue product stress. For high containment, glovebox isolators can be mounted on the side to provide safe product offloading, contained sampling, and total heel recovery for maximum product yield.

Powder Systems Ltd (PSL)
www.powdersystems.com
Systems are available worldwide

Peristaltic pumps offer contamination-free pumping capabilities

Watson-Marlow's new Bp pump features Profibus networking to the well-known benefits of peristaltic pumping, making it easy and efficient for customers to integrate this seal-less, valveless pump technology into their Profibus control system. Compared with non-networked pumps, the Bp range features Profibus compatible units that reduce engineering, hardware and installation costs, as well as offer remote diagnostics to help minimize plant downtime and maintenance costs.

Watson-Marlow
www.watson-marlow.com
Pumps are available worldwide

NIKOLAI PUNIN/GETTY IMAGES

Health Policy Challenges for Obama Administration

Jill Wechsler

White House and Congress likely to struggle over funding for bio/pharmaceutical regulation.

The calm after the heated election battle this year has been brief due to pressure on policymakers to tackle overwhelming budget issues. With Republicans maintaining tight control over the House of Representatives but losing ground in the Senate, much depends on the ability of President Obama to engineer some kind of "fix" to the mounting deficit during the year-end "lame duck" Congressional session. Healthcare policy was a key point of dispute during the election campaign, marked by promises of better coverage and predictions of soaring costs by both candidates. Now, scheduled funding cuts and significant tax increases are expected to play a large role in shaping the reform program.

The Obama victory ended prospects of wholesale repeal of the Affordable Care Act (ACA). House Republicans will continue to challenge various requirements of the healthcare legislation, but key provisions for pharmaceutical companies, such as rebates on drugs for seniors in the Part D coverage gap and authorization for biosimilars, are unlikely to change.

More broadly, the promised expansion of coverage to some 30 million previously uninsured Americans will move forward, although with consumers paying higher premiums and cost-sharing to cover ever-rising healthcare costs. That sets the stage for significant growth in the market for brand-name drugs. The Department of Health and Human Services (HHS) is working hard to meet a host of deadlines and timeframes for establishing exchanges, defining benefits, and expanding Medicaid, much of that involving states that have been reluctant to commit to these new programs in a period of political uncertainty.

Spending cuts ahead

The dark cloud looming over all these programs is the year-end "fiscal cliff," with nearly $500 billion in tax increases and spending cuts scheduled to begin Jan. 1, 2013 unless Congress acts. Executives at biopharmaceutical companies are watching closely at how tax and budget proposals will affect corporate tax rates and investment, as well as the specific funding for FDA, the National Institutes of Health (NIH), and other activities important to biomedical innovation and healthcare coverage.

All sides acknowledge the crucial need to reduce both public and private outlays for US healthcare, and drug prices and reimbursement are a prime target, particularly related to outlays for federal government health programs and Medicare Part D. House Democrats have pressed for added rebates on drugs purchased by Medicare drug plans for low-income "dual eligible" seniors, which could total more than $100 million over 10 years. There also are budget proposals on the table to reduce federal spending on drugs for federal government employees, as well as other government health programs.

The Obama victory offers some stability for FDA, as the agency continues to implement the FDA Safety & Innovation Act and struggles to find a middle ground between speeding untried new medicines to patients and protecting the public from undue risk and harm. Although there won't be a wholesale change in executive branch leadership, many top administration officials are likely to move on to other roles, and extensive cuts in the 2013 budget could undermine many FDA projects. An 8.2% cut in the FDA budget, as proposed under the sequester process, would reduce FDA's 2013 budget by $320 million and prompt the agency to lay off approximately 1000 employees, according to consultant Steven Grossman, publisher of *FDA Matters*. Even without such a severe, across-the-board cut, which could jeopardize FDA's ability to collect user fees from pharmaceutical and medical device makers, the FDA budget will remain vulnerable to pressures to reduce federal spending for some years to come.

Severe reductions in NIH funding, moreover, would jeopardize the pace of new drug and biotech discovery and support for clinical research that is key to spurring innovation needed to fill the depleted new drug pipeline. The biomedical research community is highlighting the importance of both

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Accelerate the Development of Challenging Drug Candidates via Crystal Engineering

ON-DEMAND WEBCAST

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EVENT OVERVIEW

Selection of the optimal solid form is a critical decision in the development lifecycle. It is also an effective means to overcome development challenges and accelerate the development and commercialization of small-molecule drug candidates.

Each solid-state form of an API has unique physicochemical properties that can have a profound impact on bioavailability, stability, and manufacturability. By discovering and characterizing the diversity of solid-state forms, it becomes possible to select an optimal form that displays an appropriate balance of properties that is critical for successful preclinical evaluation and product development, as well as robust manufacturing processes.

The optimal solid form such as crystal-form, salt or cocrystal can:

- Enhance the solubility and bioavailability relative to a crystalline form of the parent molecule
- Reduce pharmacokinetic variations (dose-to-dose, inter-subject and inter-species)
- Improve the stability of the API and drug product
- Increase the robustness of the manufacturing process of the API and drug product, and
- Accelerate development and commercialization

This 75-minute webcast will focus on the role of advanced crystal engineering principles and state-of-the-art screening technologies in identifying the optimal solid form of a drug candidate. You will hear about case studies using advanced screening technologies as well as the factors important to successfully manufacture the desired solid form on larger scales.

Who Should Attend:

- Pre-formulation scientists
- Material scientists
- Formulation scientists
- Formulation R&D managers, directors and group leaders
- Medicinal chemists, team leaders and directors
- Process chemists, process engineers, project leaders and directors
- Project managers
- Purchasing/procurement managers of contract services

Presented by

Pharmaceutical Technology

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Key Learning Objectives:

- Understand the basic principles of crystal engineering and its impact of solid form on drug development
- Learn about advanced screening technologies (Optiform™ Technologies) as it pertains to the design, execution and selection of the optimal solid form
- Become familiar with the API crystallization process and key considerations and desired attributes of the optimal solid form

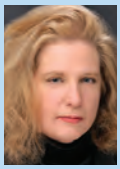
Speakers

Michael Zaworotko, PhD
Professor,
Department of Chemistry
University of South Florida

Pingyun (P.Y.) Chen, PhD
Manager of Optiform™ Technologies
Catalent Pharma Solutions

Alfred Y. Lee, PhD
Associate Principal Scientist
Merck Research Laboratories

Moderator:



Patricia Van Arnum,
Executive Editor,
Pharmaceutical Technology and *Pharmaceutical Technology Europe*

For questions, contact Sara Barschdorf at **sbarschdorf@advanstar.com**

Hot-Topic Roundup

Another push for track-and-trace

There is renewed interest in establishing a more secure national drug distribution system that can identify counterfeit and adulterated products moving through the supply chain. Congress failed to reach agreement on such a policy for inclusion in the FDA Safety and Innovation Act (FDASIA), but Senators Michael Bennet (D-CO) and Richard Burr (R-NC) have authored a compromise bill, with an eye on enactment in early 2013. Manufacturers prefer national standards to the patchwork of state pedigree and tracking polices, and want agreement before they have to implement California's comprehensive tracking requirements in 2015.

A 117-page Senate "discussion draft" establishes a national standard for tracking drug products, starting at the lot level and moving towards a future interoperable electronic unit-level tracking system. Manufacturers would identify products with serial numbers and drug codes, and there would be FDA licensure for wholesalers and third-party distributors.

Marking 1962 amendments

FDA officials and the food and drug legal community marked the 50th anniversary of the 1962 Kefauver–Harris amendments to the Food, Drug and Cosmetic Act in October 2012, noting how that law radically transformed drug development and regulation. FDA commissioner Margaret Hamburg recalled how the thalidomide disaster spurred approval of legislation that required FDA preapproval of new drugs based on safety and efficacy data. That, in turn, created a new world of randomized controlled clinical trials, human-subject protections, good manufacturing practices standards, oversight of drug advertising, and adverse drug event reporting.

Yet, these rules also led to a much longer and more costly drug development and testing process, a concern for Peter Barton Hutt, senior counsel at Covington & Burling and FDA counsel back in 1962. Hutt sparred with Bob Temple, Center for Drug Evaluation and Research (CDER) deputy director for clinical science, at a commemorative reception sponsored by the Food and Drug Law Institute: Temple insisted that FDA is very flexible in accepting a range of data to support new drug approvals, while Hutt complained that the review process is too long and burdensome. They agreed, though, that comparable changes in the FD&CA are not likely any time soon.

Extending expiration dates

Critics of pharmaceutical companies are looking to extend labeled expiration dates as a way to reduce spending on prescription and over-the-counter (OTC) medicines. Three Missouri consumers recently filed a lawsuit claiming that too-short shelf-life limitations merely help manufacturers boost sales. While the plaintiffs acknowledge that drug expirations are based on required stability tests, they propose that company testing should extend those dates—not keep them as short as possible. Similarly, a letter in the *Annals of Internal Medicine* in October cites research demonstrating that many long-expired OTC pain medications remain effective. The study tested 14 drug compounds and found that 12 had concentrations at least 90% of the labeled amounts. FDA and the Department of Defense have a Shelf Life Extension Program (SLEP) to support longer use of drugs in medication stockpiles, and that could provide a basis for extending expiration dates more broadly.

FDA and NIH in protecting public health for patients at home and around the world.

Congress tackles compounding

Meanwhile, mounting deaths from contaminated steroid injectables made by a Massachusetts compounding pharmacy are focusing attention on the need for broader FDA legal authority in this and other areas. The need to reauthorize animal-drug user fees in 2013 is expected to provide a vehicle for legislation that would better secure the prescription drug supply chain and also address drug compounding oversight. (For more information on this subject, view "Compounding and FDA Regulation" on www.pharmtech.com/pharmtechtv.)

The ongoing fungal meningitis outbreak had sickened more than 425 individuals and caused over 30 deaths, as of early November. Rep. Edward Markey (D-MA) has proposed legislation to enhance FDA oversight of compounding pharmacies, and lead House and Senate committees held hearings right after election day to address the

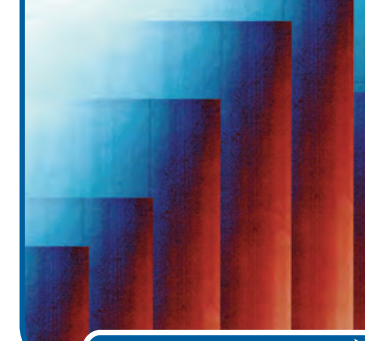
response by FDA and state regulators and to analyze actions by the offending compounder, the New England Compounding Center (NECC). Markey's bill clarifies FDA's right to inspect and regulate large compounders that qualify as drug manufacturers. Small compounding pharmacies would continue to operate under state licensing, and FDA could issue waivers to operators responding to drug shortages and public health crises. Compounded drugs have to be labeled that they have not been tested for FDA safety and efficacy standards, and FDA has to publish a list of unsafe or ineffective drugs not suitable for compounding.

FDA regulation of compounders has been a thorny issue for decades, as previous efforts by the agency to impose stricter rules on compounders have been struck down by the courts. But the recent crisis has reopened the debate over the adequacy of state versus federal regulation of pharmacies and when compounding qualifies as drug manufacturing.

Efforts by FDA and Massachusetts regulators to shut down NECC and its sister company, Ameridose, highlight the links between drug shortages and compounding. FDA Commissioner Margaret Hamburg noted that the agency is working hard to minimize shortages in important Ameridose products used in surgery and to prevent congestive heart failure. Yet, former FDA official Scott Gottlieb also commented that too-tight FDA regulations have led to shortages of low-cost injectable drugs, prompting hospitals and patients to seek alternatives from compounders. Too-low reimbursement for generic injectables also may limit pharmaceutical industry interest in producing these therapies, leading to shortages and greater reliance on compounders.

KV Pharma weighed in that the NECC case illustrates FDA's error in permitting compounders to continue to produce hydroxyprogesterone to prevent premature births after approving KV's Makena. State health agencies and insurers have been opting for the less costly compounded version, but now may shift to the KV product to avoid exposure to possibly unsafe compounded medicines.

There will be further debate over how much added legal authority FDA needs to deal with compounders. Some agency critics complained that FDA did not make full use of its existing legal authority to regulate NECC following initial unsatisfactory inspections. Republicans generally oppose giving the agency stronger legal powers, and compounding pharmacies claim they are sufficiently regulated by state licensing boards. Pharmacists object to the Markey bill for imposing too-broad FDA regulation of compounding that could block patient access to needed medicines and further overtax FDA. It's a cost-versus-safety issue, and a challenge to find a compromise that passes muster. **PT**



PHOTODISC/GETTY IMAGES

Time to Revise ICH Q9

Lynn D. Torbeck

A change in terminology could emphasize patient protection.

The current International Conference on Harmonization (ICH) Q9, *Quality Risk Management* guideline was recommended for adoption by the three regulatory bodies of the United States, Japan, and the European Union on November 9, 2005 (1). The guideline's Expert Working Group (EWG) is to be commended for the content and quality of the current version.

The EWG's success is evidenced by the ready adoption by pharmaceutical companies, the industry in general, and by the many public presentations, training courses, and journal articles. Almost all pharmaceutical companies have a quality-risk management (QRM) program at some stage of development. The close relationship of ICH Q9 with ICH Q8 *Pharmaceutical Development,* and ICH Q10 *Pharmaceutical Quality System* has further solidified wide spread utilization of QRM in practical applications.

QRM and patient protection

Despite ICH Q9's success, it could benefit by revisions that place a stronger emphasis on minimizing risk to the patient rather than managing risk of quality. The current Q9 borrowed extensively from ISO/IEC Guide 73:2002 and has incorporated much of the format and concepts in ISO/IEC Guide 73:2002 (2). QRM, by implication, is internally focused, but there is a need to add an external focus to further minimize risk to patients.

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ICH Q9 does comment on the role of the patient in the structure of the QRM program, but that context is limited. It is implied, but not actually said, that QRM means management of risk to the patient. The word patient occurs only seven times in the document; twice the patient is referred to as a stakeholder, twice regarding protection of the patient, once as an interested party, once regarding patient need, and once regarding high-quality drugs. Patient and risk are not mentioned together. By contrast, the phrase "Quality Risk Management" occurs 81 times.

It is assumed that the EWG intended that QRM would reduce risk to the patient, but the majority of industry readers may not recognize that assumption and may implement Q9 with an emphasis on management rather than on risk to the patient; obviously two different goals.

Q9 needs to be more explicit in its goal of patient risk minimization (PRM). This can be achieved by simply replacing the words "quality risk management" where they occur in the current version with "patient risk minimization." The shift from quality to patient and from management to minimization would refocus the entire quality program from internal to external and would further support the lifecycle concept of validation.

The risk to quality would still be managed by minimizing the risk to the patient. For example, a sentence in Q9 reads: "… the protection of the patient by managing the risk to quality should be considered of prime importance" (1).

Now consider the focus of this restatement: "The enhancement of quality by minimizing the risk to the patient should be considered the prime objective." Notice how this change shifts the focus from risk management to risk minimization. This revised statement has the additional benefit of implying continuous improvement and not just maintaining the *status quo.*

The shift from static management of quality to continuous reduction in patient risk, suggests the addition of statistically oriented tools and concepts. A new version would benefit greatly with these statistical inclusions:

- definitions of probability for frequentists and Bayesian theory
- a short review of how frequentists and Bayesian analysis differ
- a note that in the field of statistics risk is often just a probability value
- a short review of the decision risks as defined by Type I and Type II hypothesis errors
- a short review of sampling risks as defined by acceptable quality limit (AQL) and by the limiting quality (LQ).

Note that in the field of statistics, the Type II error and the LQ are associated with the concept of patient or consumer risk. Minimizing these risks is inherent in good data design, collection, and analysis.

Conclusion

It is an opportune time to sharpen the focus on patient risk now that a measure of success with quality risk management has been achieved. Replacing the term "quality risk management" with "patient risk minimization" is one way to move to the next level of patient protection while building on the current strong base of ICH Q9.

References

1. ICH, Q9, *Quality Risk Management* (2005).
2. ISO/IEC Guide 73:2002. **PT**

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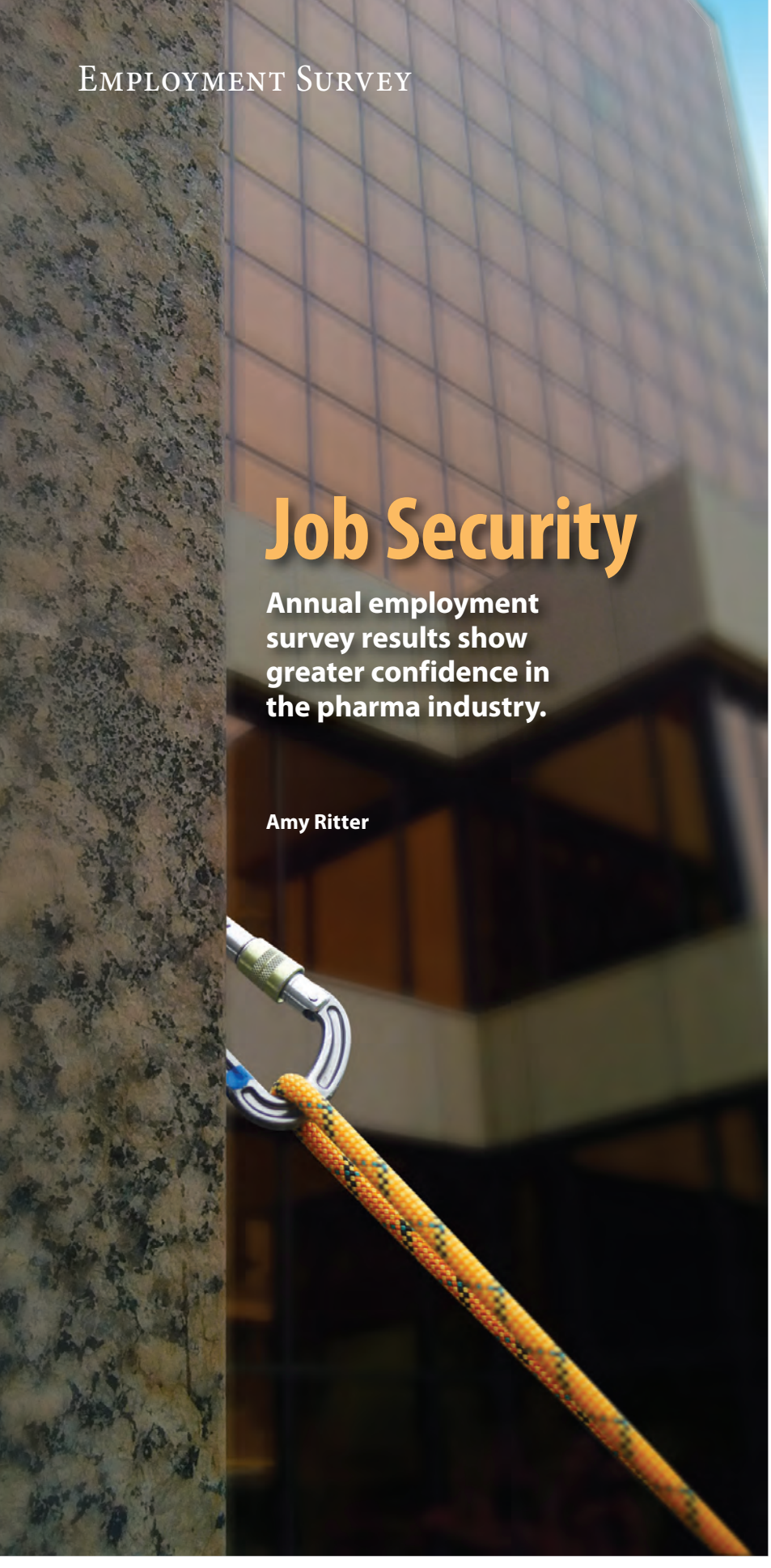

Job Security

Annual employment survey results show greater confidence in the pharma industry.

Amy Ritter

The spate of large mergers that dominated the news a few years ago seems to be slowing, but bio/pharmaceutical companies still face pressure to run leaner businesses and to see a better return on investment from their R&D divisions. The global economy continues to limp along, and pharma faces pricing pressure from cost-conscious payers and from developing countries determined to hold the line on drug prices. The industry continues to adapt to this challenging business environment, and these challenges cannot help but affect pharma employees. *Pharmaceutical Technology* asked readers about their employment situations: how secure they felt in their positions, how satisfied they are with their jobs, and how they see the future of their companies and the global industry. The following pages highlight key results from the survey.

The level of employment insecurity is dropping among biopharma employees. Year over year, fewer respondents say they feel less secure in their positions than they did the year before. In 2010, 53% said they felt less secure. This dropped to 41% in 2011, and this year, only 34% were feeling less secure. While this seems encouraging, readers did not say they felt more secure. Instead, an increased percentage (47% this year) said they felt about the same as last year. It seems, then, that pharma employees are becoming accustomed to the new, more fluid business environment. Is insecurity becoming the new normal? Perhaps, but respondents felt confident they would be able to find a new job if they had to, and they continue to derive satisfaction from the intellectual stimulation and challenging projects associated with their jobs.

The difficult economic climate is being felt by those in the industry. A third of respondents, 33%, indicated that business had declined over the past year. Yet, respondents were upbeat about the future, both for their own companies and for the industry as a whole. Only 34% expect business at their own companies to decline next year, with the rest expecting either no change (18%), or an increase (48%). When asked about the industry as a whole, 49% said they expected business to improve. Next year will bring its own set of challenges for the industry, but let's hope that this optimism is well founded.

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WHEN YOU NEED TO BE SURE

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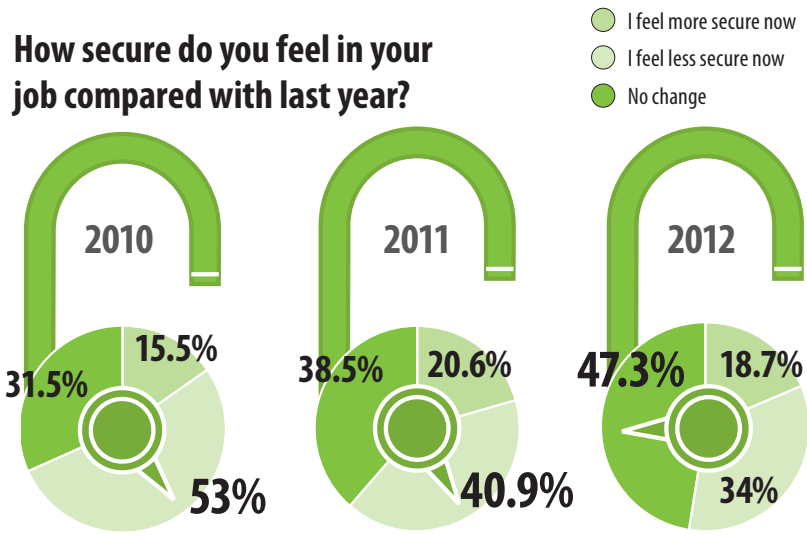
Employment Survey

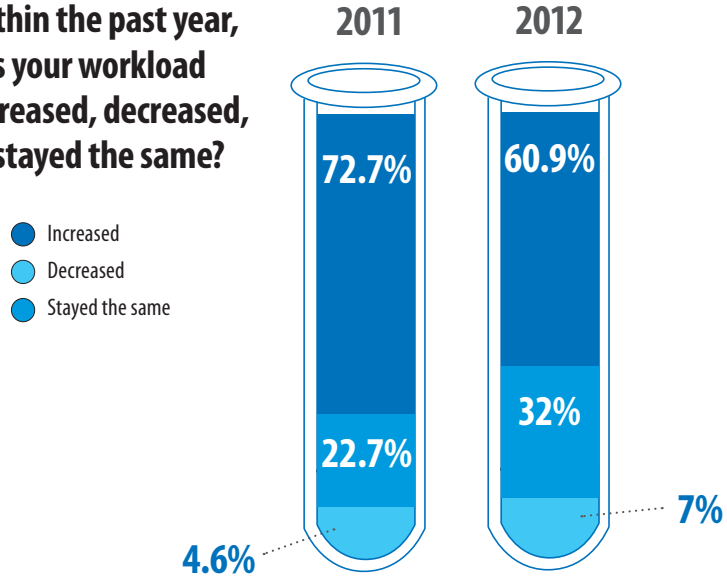
How secure do you feel in your job compared with last year?



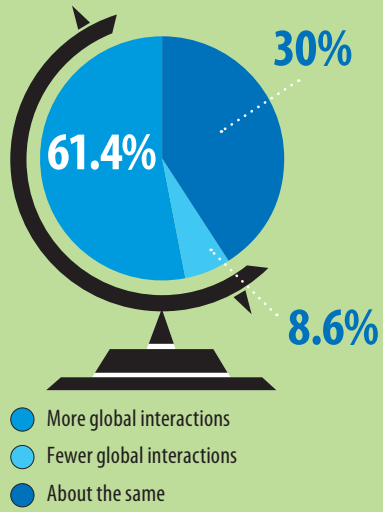
If it was necessary for you to change jobs this year, how would you assess the job market?

10.8%	It would be straightforward to find a job comparable to the one I have now.
44.6%	It would take a while, but I would be able to find a job comparable to the one I have now.
19%	It would be straightforward to find a job, but it probably wouldn't be as good as the one I have now.
25.7%	I would have to search hard, and be prepared to take what I could get.

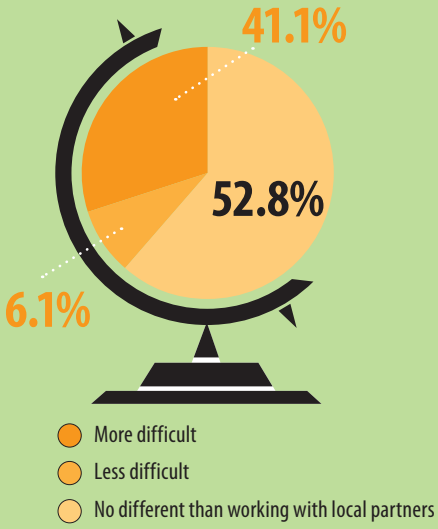
Within the past year, has your workload increased, decreased, or stayed the same?



Has your job become more global in nature (i.e., more offices/sites and/or partners in other countries) over the past two years?



Has having offices/partners in other countries made your job:



How do you communicate with other offices or partners in other countries (check all that apply)?

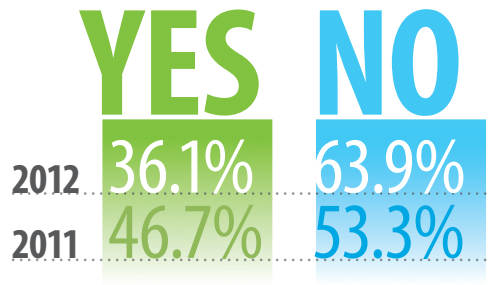
- Email 98.9%
- Teleconference 82.8%
- In-person visits 54.7%
- Skype or other streaming video 22.5%

This is the **main reason** I come to work

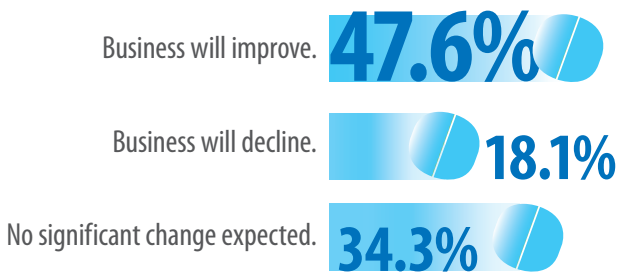
MEDIAN SALARIE$

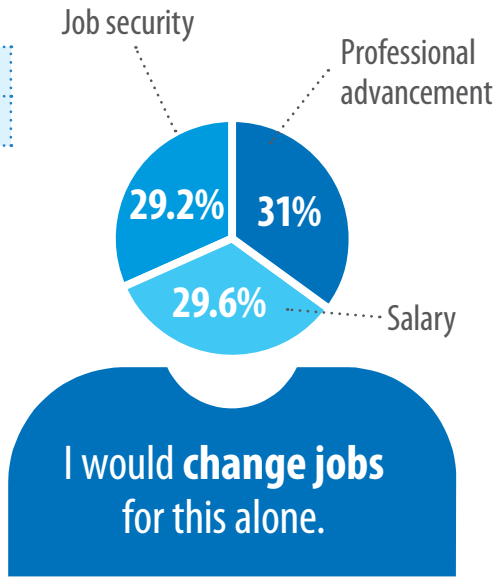
US (USD)	105,000
Canada (CAD)	104,500 (104,544 USD)

In the past two years, have you been through a merger, acquisition, downsizing or restructuring?

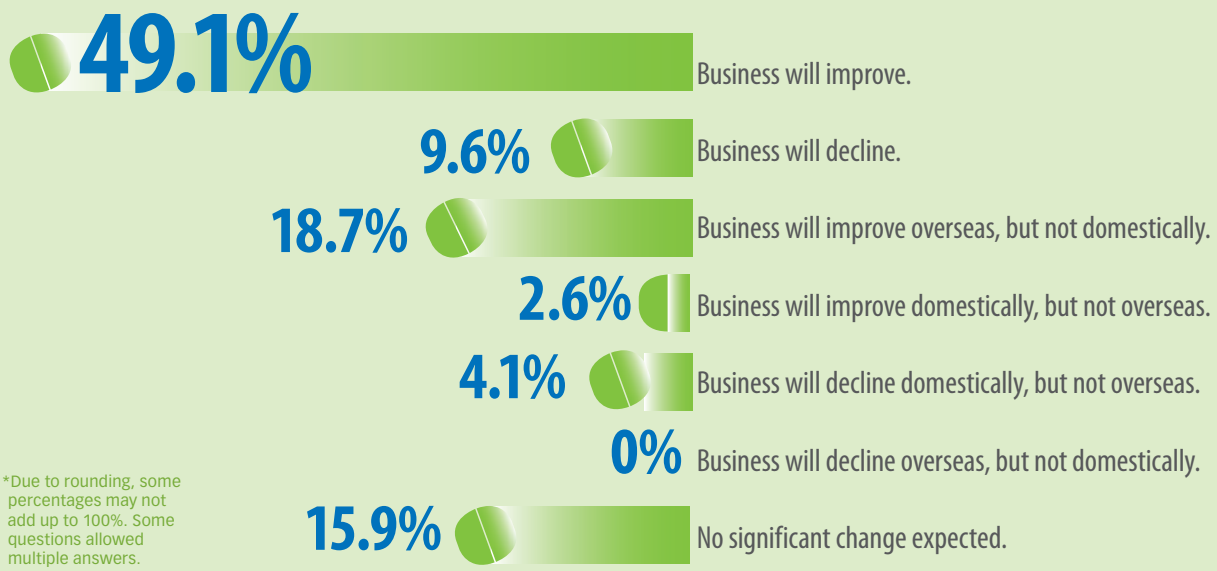


What is your prediction for your company's business prospects in the coming year?



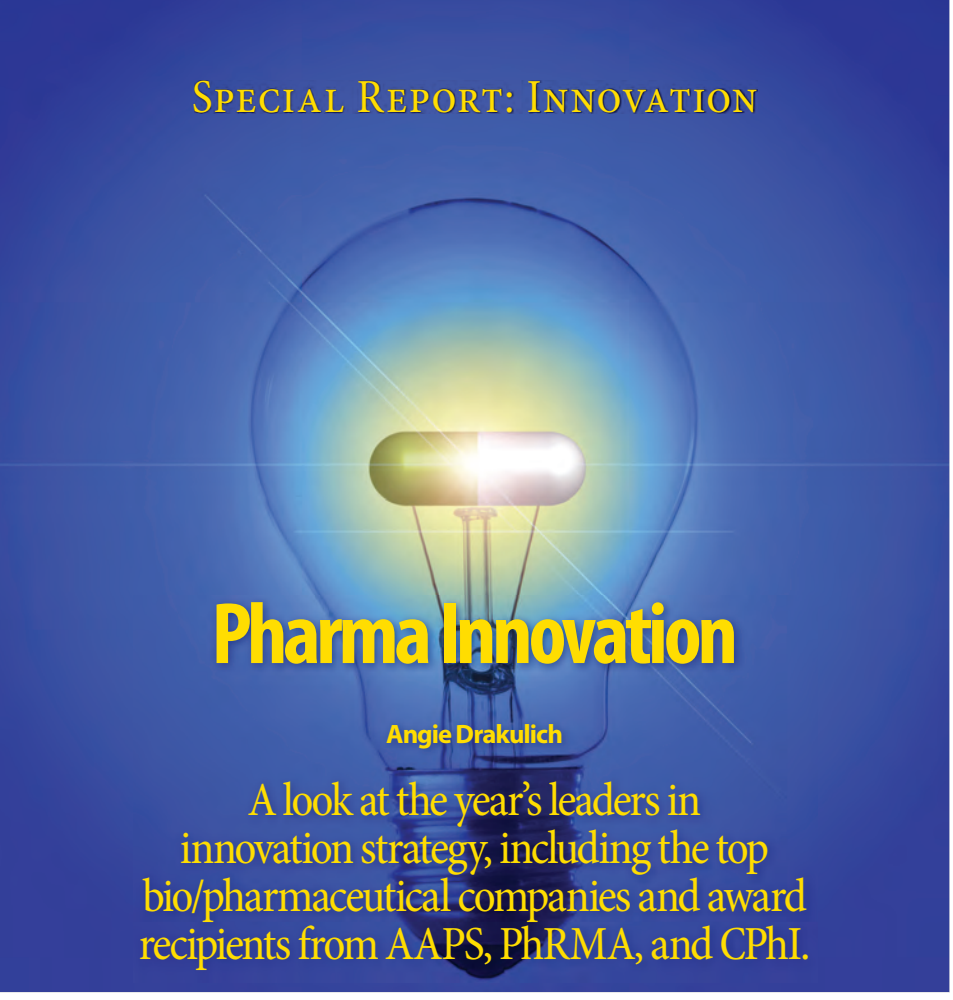


In your view, what is the general outlook for the bio/pharmaceutical industry in the short- and long-term?



*Due to rounding, some percentages may not add up to 100%. Some questions allowed multiple answers.

GRAPHICS: MELISSA MCEVOY



Pharma Innovation

Angie Drakulich

A look at the year's leaders in innovation strategy, including the top bio/pharmaceutical companies and award recipients from AAPS, PhRMA, and CPhI.

"Innovation." This word is at the heart of bio/pharmaceutical development and manufacturing, whether innovators are targeting a new cell line or formulation, a drug delivery target or method, an analytical or packaging approach, or a quality system. As FDA Commissioner Margaret Hamburg said in April of this year at the Boston NEHI conference on "Bridging the Innovation Gap," innovation "is an issue that is important to us all, whether you come from industry, from academia, from clinical practice, or from government." She spoke about the challenges facing R&D and product pipelines, including patent-cliff implications, stating that, "The trend lines for innovative products relative to investments in research and development are not what any of us would like."

As an example, Hamburg pointed to the current "golden age" of biomedical discovery in which the industry has sequenced the human genome to reveal potential drug targets and made gains in high throughput screening and nanotechnology, and yet has not necessarily translated these developments into therapies or cures. Hamburg proposed in her speech that a potential solution to this innovation gap requires a "comprehensive, integrated strategy that engages the full 'eco-system.'"

Such a strategy would include "new and strategic investments in research," and "true collaboration by stakeholders," including "strong leadership from business, academia, and government," she said.

Here, *Pharmaceutical Technology* looks at some of the collaborative efforts taking place among these stakeholders to continue to advance innovation in drug development and manufacturing. The following pages highlight honors given to graduate students and professors as well as bio/pharmaceutical R&D and manufacturing teams throughout 2012. As we prepare to enter the year 2013, we hope these individuals and their hard work will provide inspiration for further pharma innovation.

DRUG-PRODUCT INNOVATION STRATEGIES AMONG BIG PHARMA

Every year, our sister publication *Pharmaceutical Executive* publishes a report on the top 50 pharmaceutical companies based on global sales of prescription drugs. These companies have managed to stay ahead of the game as the industry faces multiple patent expiries and a changing landscape that includes new outsourcing models, capacity-sharing, and consolidation strategies.

As we look ahead to 2013, *Pharmaceutical Technology* asked the top companies in this list to talk about their innovation strategies, with a specific focus on drug development and manufacturing. These companies include, in order: Pfizer (New York) with 2011 global prescription sales of $57.7 billion; Novartis (Switzerland) with sales of $54 billion; Merck (New Jersey) with sales of $41.3 billion; and Sanofi (France) with sales of $37 billion. Below are their responses.

Pfizer

Kevin Nepveux, vice-president, Global Technology Services, Pfizer Global Supply

"Innovation is a mindset, not a process that can be turned on and off. Organizational strategists tell us that behaviors eat process for breakfast, yet the tendency to separate 'hard' technical skills from the 'softer' communicative skills that drive global workforce interaction persists. Technical-based organizations continue to place great value on the 'hard' skills. We instead need to better understand how our technologists interact with each other, our businesses and their environmental challenges to inspire the everyday innovations as well as breakthroughs.

"In 2010, Pfizer Global Supply (PGS) reexamined its approach to innovation. We'd designed our tactics to inspire creative thinking, but our follow-up metrics included chasing after projects' monetary value. We began to see the categorization of projects as innovative to meet the fiscal metrics, rather than the unleashing of a mindset to derive truly creative solutions. It was time to reinvigorate our innovation methodologies.

IMAGE: DAN WARD; BUENA VISTA IMAGES/GETTY IMAGES

"We conducted a year-long listening tour at our manufacturing locations and with our technical groups. We formed a diagonally hierarchical global team to steer the development of the new approach, with executive team sponsorship and participation, a manufacturing mechanic operator, technologists, and the organizational levels in between—all with equal seats at the strategy table.

"Today, our deliberately small headquarters' innovation office trains innovation coaches around the world. This 200-plus global network has responsibility to build local innovation ecosystems and to adapt innovation tools to local needs and cultures. Rather than being in the business of innovation, innovation is instead employed at the needs of the local business.

"The ideas need to come from everywhere within our global organization, but innovation must be nurtured from the top. Sure, we still need to show the fiscal value of all of this effort. However, we have seen significant payback in a short time by shifting our focus to changing the innovation mindset first, and to allow value to emerge as an outcome of a new way of thinking and behaving. The PGS technologists of tomorrow are not the same mold as the past, and neither is our business."

Novartis

Timothy Wright, global head of development

"There is a consensus in the pharmaceutical industry that we need to accelerate the pace of drug development. If we fail to do so, we won't keep up with the rising health challenges facing our society. Novartis has made good progress with some strong shifts in our approach to drug development. One shift is to invest in developing multiple indications simultaneously (rather than serially), where we advance compounds in more than one clinical setting in parallel, thereby increasing the likelihood that drugs get to patients faster. Once you understand the disease biology and the molecular pathways involved, then each compound can be tested simultaneously in multiple diseases that share the same pathway. An example is our mTor inhibitor everolimus, which is now approved in the US for five cancer indications (under the tradename Afinitor) and renal transplantation (under the tradename Zortress), and our orphan drug Ilaris, originally approved in a very rare genetic disease and now continues to be developed in larger disease populations, including gouty arthritis and heart disease.

"Another solution to tackling the innovation drought is collaboration and knowledge-sharing. The cost of developing a drug has risen exponentially. Currently, it takes an average of 10 years and costs on average $4 billion to bring a new therapy to market. This model is not sustainable. We need to work together across industry, academia, and government to make our innovation dollars work harder. Only by working together can we make sure new and innovative treatments get to the patients who need them the most."

Merck

Rich Tillyer, senior vice-president, Discovery & Preclinical Sciences, Merck Research Laboratories

"The opportunities for Merck and the pharmaceutical industry to impact human health are real and numerous given the continuing rapid evolution of biomedical science, but this rapid evolution will not happen without a continued investment in R&D and emphasis on innovation. Innovation in R&D is a critical success factor and Merck understands that this requires a long-term commitment.

"At Merck, our focus lies in developing first- and best-in-class medicines that will make a meaningful difference for patients. To realize this goal, we need to establish a culture of innovation fueled by collaborations with internal and external partners, and with a focus on growing talent. We will continue to drive these initiatives in 2013 and beyond to ensure that our pipeline of candidates remains strong and continues to ad-

Innovation in a leading disease target: Alzheimer's

Earlier this fall, the Pharmaceutical Research and Manufacturers of America (PhRMA) honored nine individuals for their research into and fight against Alzheimer's Disease (AD) as part of the association's Research and Hope Awards. The awards were launched in 2012, and replace the organization's Discoverer's award program. PharmTech was a media partner of the awards. What's interesting about the group of winners is that the recipients include not just scientists and researchers, but also patient advocates and volunteers. PhRMA President and CEO John J. Castellani refers to the four award categories as the "ecosystem" required to treat, prevent, and defeat AD once and for all. "Each one of these recipients brings a perspective that is necessary for success when you are trying to battle a disease like Alzheimer's," he said.

The Research & Hope Award for Academic Research in AD went to Bradley T. Hyman, MD, PhD, professor of neurology at the Massachusetts General Hospital/ Harvard Medical School, and to David Holtzman, an Andrew B. and Gretchen P. Jones Professor and Chairman at the Washington University School of Medicine's Neurology Department.

Holtzman, who has been working on AD issues in various capacities for approximately 20 years, believes that the most promising area in terms of targeting a preventive drug or therapeutic drug are to make a long-term impact on the disease. "The genetics, biochemistry, animal model work, clinical/pathological data, and biomarker data still suggest that targeting the buildup and accumulation of amyloid-beta and tau in the brain remain the most promising targets." His laboratory is working on ways to better understand these findings associated with the sleep-wake cycle influencing the onset of amyloid-beta accumulation in the brain . . .and better ways to target the tau protein.

Hyman adds as a promising area the "recent ability to detect pathological changes well before clinical symptoms. It is this ability to tackle the disease early that I think will give us the leg up to prevent the illness rather than 'cure' it," he says.

The Research & Hope Award for Biopharmaceutical Industry Research in AD went to the Merck BACE Team, including Eric M. Parker, executive director and neuroscience site lead; Andrew W. Stamford, director of discovery chemistry; Matthew E. Kennedy, associate director of neuroscience; Mark S. Forman, director of clinical research; and Julie A. Stone, senior scientific director.

The BACE team has been evaluating the safety and efficacy of the beta-amyloid precursor protein site cleaving enzyme, or BACE, inhibitors, including MK-8931, which is Merck's lead AD pipeline compound. Clinical-trial results thus far associated single doses of MK-8931 with marked reductions in Aß peptide concentration levels.

"The amyloid hypothesis suggests that one of the ways to alter the molecular cause of AD is to inhibit the activity of BACE. With these so-called BACE inhibitors, the production of Aß proteins would be stalled, thus possibly impacting the onset of AD," explains Parker. "Despite several investigational compounds and monoclonal antibodies that have tested the amyloid hypothesis with little if any success, we believe that BACE inhibition represents a hopeful approach for AD patients. We have shown that BACE inhibition reduces levels of the Aβ peptides to a greater degree than other treatments that have been tested. Therefore, BACE inhibitors are a promising means for testing the amyloid hypothesis. That said, however, we are equally dedicated to finding non-amyloid approaches and symptomatic therapies for AD, and are continuing our research in those areas," he adds.

The Research & Hope Award for Patient Advocacy went to Kate Maslow at the Keck Center Institute of Medicine (IOM). Maslow, a scholar-in-residence at the IOM National Academy of Sciences, has been focusing on issues tied to the care of people with AD and other dementias. Maslow has a unique perspective on how academia and industry can better partner with healthcare workers and those engaged in day-to-day AD patient care to improve patient outcomes and treatments. "Sometimes, academic and industry researchers are disconnected from the everyday experience of people with AD and other dementias and their families. While these researchers know, at least in theory, how the conditions affect the person and family and may have relatives who have the conditions, the search for biomedical treatments, biomarkers, and imaging technologies can isolate them from the ultimate purposes of that search," she says. "It is possible that more contact and interaction among people with the conditions, families and academic and industry researchers would result in new understanding and ideas that might help to focus the research effort."

Maslow is certain to add, however, that communication goes both ways. "Some people with the conditions, families, and advocates would benefit from a more sophisticated understanding of the ongoing research effort, the complexity of the conditions, and the difficulty of isolating the causes and effective treatments. Much of the publicly available information about these issues is oversimplified."

The Research & Hope Award for Volunteer Champion went to Neha Chauhan at the AFA Teens for AD Awareness. Chauhan has been volunteering in the fight against AD since age 15 as the founder of AFA Teens, which is an active branch of the AD Foundation of America dedicated to youth advocacy. Today, says Chauhan, AFA Teens has an advisory board of teenagers from across the US that provide insight on how teens are being affected by the disease. In addition, approximately 1200 college-bound students apply for the organization's essay scholarship contest each year. Chauhan is currently an MBA student at Stanford. "I hope that whatever career path I choose will help make sure that AD is a distant memory one day," she says.

Looking ahead , each award recipient has high hopes for the future of AD research and care. Maslow says she would like to see "the development and availability of biomedical treatments that could prevent and/or delay the onset and progression of AD disease." Government policies that enable healthcare systems to identify and evaluate cognitive impairment in patients/enrollees while delivering ongoing medical care and support are also on Maslow's wish list.

Holtzman agrees that the amount of partnerships between academia and the industry need to increase and notes that such projects are on the rise, such as the AD disease neuroimaging initiative as well as in prevention trials in dominantly inherited AD disease. "They are also partnering via research projects at the level of individual groups of labs with specific companies," he says.

These hopes for the future AD research and patient care are key, especially considering some of the clinical-study setbacks that have occurred over 2012 (Johnson & Johnson, Pfizer, and Eli Lilly all released reports of failed clinical trials targeting the beta-amyloid protein). Some reports have stated that people are giving up hope as well as research funds towards curing AD as a result.

Parker responds: "Many of the latest setbacks...can be attributed to at least two factors. First, the treatments being tested had significant side effects that limited the doses that could be administered, which may have also limited their effectiveness. Second, these studies have reinforced a collective opinion in the field that we may need to start treatment years before patients begin to show symptoms. However, that means being able to identify people who are at risk for developing AD in the first place, and that research is still ongoing."

Hyman adds, "The problem [of AD] is too immense—with 6 million Americans already affected and $200 billion in care costs—to give up just because the first few attempts did not succeed. We don't know if the drugs that have been tried were given too late, in too low a dose, or simply whether more powerful combinations of drugs must be given. Our understanding of the disease process has come too far to consider giving up now as an option."

To listen to the full interview with Castellani, visit PharmTech.com/PharmTechTV. To read the full interview with the BACE team, log onto PharmTech.com. The full bios of the winners are at www.phrma.org/awards. —*Angie Drakulich*

vance toward the patients who need our medicines."

Sanofi

Marc Bonnefoi, head of the Sanofi North America R&D Hub

"Sanofi is evolving its R&D approach to be able to access the best ideas, science, and people in research. This requires a combination of both internal and external innovation and is implemented through the creation of geographically focused integrated research hubs in which Sanofi scientists increasingly partner with external teams. R&D hubs have been created in North America, with a special emphasis in the Boston area, as well as in Germany and Asia, and a project for implementing a hub in France is being discussed.

"For many years, the pharmaceutical industry designed drugs from biological targets that were not always well validated and in areas where the path to clinical proof-of-concept and ultimate validation in patients was uncertain. We screened scores of molecules to see whether they had any effect on different disease models that were often incompletely qualified. There were too many assumptions regarding the biology of diseases. Today, we seek to begin with an understanding of the underlying cause(s) of a given disease and work to develop a solution to interfere with that process.

"We are trying to integrate a translational approach to these efforts, applying the knowledge from patient populations and medical experience much earlier in the R&D processes. To make these translational research efforts a reality, Sanofi is using the ability to translate to the patient situation as a yardstick to judge the quality of projects. None of this can be done by Sanofi R&D alone: we have great people and fantastic ideas, but no one organization can single-handedly tackle the complexity of human chronic diseases, which remain beyond our reach at the moment. By effectively implementing open innovation and raising the bar for projects to be accepted into development and reach further investment milestones down the road, Sanofi expects to create one of the best portfolios in the industry."

STUDENT INNOVATION ACROSS THE PHARMA SCIENCES

At the 2012 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting in Chicago, graduate students across the country were honored for their research and work in bio/pharmaceutical innovation. Symposium awards were given to graduate students in the areas ranging from analysis and pharmaceutical quality to ocular drug delivery and disposition. *Pharmaceutical Technology* had the chance to talk with a few of the recipients about their work.

Biotechnology category winner David W. Woessner noted that his team's work

at the University of Utah on "Synthetically Lethal Combinations for Chronic Myeloid Leukemia (CML) Therapy-Disrupting Dimerization of Bcr-Abl and Secondary Leukemia Specific Pathways" demonstrates the first development of a protein/peptide-based therapeutic for CML.

"While current therapies in the clinic (tyrsosine kinase inhibitors [TKIs]) act on the ABL portion of the protein, we are demonstrating efficacy by targeting the BCR portion, necessary for oligomerization and activation of the tyrosine kinase. Additionally, this work also exploits a combination therapy approach early in development," he said. Future research in this area has already moved towards combination therapy approaches, explained Woessner. "There are now essentially five TKIs that effectively treat CML. Combinations with other small molecules that target leukemic stem cells, but not normal/healthy hematopoietic stem cells are highly valued. We will continue to see trials for drug combinations," he said.

Mamta Kapoor of the University of Connecticut also won in the biotechnology category. Her research, "Elucidation of Cellular Uptake Mechanism of Novel Ternary Anionic-siRNA Lipoplexes," aimed to obtain an understanding on formulation-cell interaction that may facilitate faster formulation optimization to achieve efficient delivery. "This research area is interesting because it involves a mechanistic approach to comprehend the rate-limiting steps to proficient intracellular delivery of therapeutic agents," Kapoor explained. The mechanistic studies "have helped in understanding the contribution of formulation components in the uptake process and consequent bioactivity." Looking ahead, Kapoor's team intends to repeat the studies with other novel formulations.

Lakshmi Prasanna Kolluru, who won in the drug design and development interface category, focused on the "Design and Development of Albumin-based Theragnostic Nanoparticles for Tumor Targeted Drug Delivery." Based at Mercer University, the PhD candidate was inspired as a teenager by a cousin, a cancer patient suffering from the side effects of chemotherapy. "She was disturbed psychologically when she had lost her hair due to side effects and this spurred the interest in me to focus on cancer research. So, when my professor gave me the freedom to design a project, I opted to work on development of a delivery system that targets anti cancer drugs to tumor and reduces the side-effects of chemotherapy," said Kolluru. Looking ahead, the grad student says the university team is "planning to decorate this delivery system with dual-targeting probes to examine the efficacy of the targeting ligands *in vitro* and *in vivo* for selective localization of the drug in the tumor region."

Jiban Jyoti Panda of the International Center for Genetic Engineering and Biotechnology in New Delhi and of the FM University of Balasore, Odisha, India, won in the category of formulation design and development for the paper, "Self-Assembled Dipeptide Nanotubes, Nanovesicles and Nanogels: Potential Vehicles for Targeted Tumor Drug Delivery." The research focused on testing the potential of nanotechnology in cancer therapy. "Different types of polymeric, inorganic, and metallic nanoparticles have been investigated for their potential for effective tumor

Recognizing Pharma Innovation at CPhI Worldwide

Innovation in technology that supports drug development and manufacturing to meet the evolving needs in pharmaceutical products is crucial. The CPhI Pharma Awards recognize such innovation and were given at CPhI Worldwide, the large exhibition of contract manufacturers and providers of pharmaceutical ingredients and related technology, organized by UBM Live, and held Oct. 9–11, 2012, in Madrid. Formerly known as the Innovation Awards, the rebranded CPhI Pharma Awards featured Gold, Silver, and Bronze winners for the Best Pharma Innovation. The awards were designed to encourage entries in diverse areas, including formulation development, drug delivery, chemical manufacturing of APIs and intermediates, and biomanufacturing.

Earning the Gold CPhI Pharma Award was Haemopharm Healthcare, a Milan-based manufacturer of flexible bags for sterile solutions and related containers and components. Haemopharm was recognized for its needleless injection vial (NIV), a needle-free vial-closure system that can be used on products supplied in a glass or plastic vial, whether in a liquid, gel, or powder form. The NIV system maintains sterility and avoids contamination due to a hermetically reclosable seal. The reclosure avoids back flow and leakage of contents.

Merck Millipore, the life-sciences division of Merck KGaA, won the Silver CPhI Pharma Award for its bimodal silica as a drug-delivery platform, which is designed to facilitate solubility enhancement of poorly soluble APIs. Merck Millipore's innovation takes advantage of the two-fold pore structure of silica, which offers a large surface area and good transport properties for drug delivery. In October 2012, Merck Millipore announced the availability of a range of products for enhancing drug bioavailability and addressing other challenges in pharmaceutical formulation. These offerings include products that address solubility and pharmacokinetic and pharmacodynamic modification and targeting, which must be taken into account for optimizing bioavailability of the final drug.

The Bronze CPhI Pharma Award was given to BioClin, a pharmaceutical company based in Delft, The Netherlands, for its Multi-Oral Remin remineralization gel, a product, which is applied in the oral cavity to treat and prevent bleeding gums and tooth erosion. The formulation is based on a 2QR-complex, an acetylated polymannose complex, which blocks the adhesion of bacteria, neutralizes them, and combines this activity with the remineralization effect of antiplaque properties.

Although not placing in the top three, there were two other finalists to the CPhI Pharma Awards. The finalists were Linhardt, a Germany-based provider of packaging systems, for its Multiflex collapsible tube technology, which is designed to improve traditional laminate tubes, and YaoPharma, a generic-drug company based in Chongqin, China, and a subsidiary of Fosun Pharmaceutical, for alprostadil, a lyophilized emulsion for injection.

The CPhI Pharma Awards also recognized advances in sustainability, which included a new award for Best Sustainable Packaging, which recognized a company for a specific material, machine, or process that facilitated sustainable packaging. The award went to MeadWestvaco Healthcare for its adherence-enhancing drug packaging, which consists of a recyclable tear-resistant outer carton and an easy-slide blister with a calendar integrated to aid patients in tracking their medication.

For additional information on the CPhI Pharma Award winners, listen to our podcasts at www.PharmTech.com/PharmTechTV.

delivery and therapy. However, there are many factors which prevent the development of these nanoparticles for safe human use," Panda explained. "We tried to develop peptide-based nanoparticles, which are expected to be highly biocompatible due to their peptidic origin. Moreover, because the greatest problem with peptide-based drugs or systems is their low *in vivo* stability, we tried to develop nanoparticles from designed small peptides with the modified amino acid α,β-dehydrophenylalanine (ΔPhe), residue, which is unique and would provide the nanostructures with enhanced assembling behavior and resistance to enzymatic degradation leading to better stability."

Panda's next goal is to demonstrate the efficacy of these systems in other tumor models and to prove their broader application potential, such as peptide-based nanosystems that may target tuberculosis, AIDS, and other global diseases.

University of California–San Francisco student Rachel Jean Eclov won for her research into "*In Vivo* Characterization of ABCG2 Enhancers," in the category of pharmacokinetics, pharmacodynamics, drug metabolism, clinical pharmacology and translational research. "Previous research on MXR functionality has been mostly aimed at functional (coding) variants of MXR. My research is unique in that it looks for how other types of genomic variations can alter MXR expression and thus drug disposition. I utilize epigenetic tools to unravel how MXR expression can be tissue specific or transiently increased or decreased," she explained.

"I then consider how genetic variation in identified regulatory elements can alter the transcriptional properties of that element. Although other epigenetic research has been published, the majority of it is on variations in regulatory elements that cause developmental defects. My research uses epigenetics to identify genetic variations that impact the more subtle world of drug disposition where the effects of these variations are not as obvious but can be just as severe." In terms of how Eclov's research may affect future industry work, she says, "Even though my research is only at the initial edges of understanding of the genetic regulation of an ADME gene, it can be used as a general template for others to research the genetic regulation of their own gene of interest. It shows that there are many ways a gene's expression can be epigenetically regulated and thus deregulated in cancers or by drug treatment. It is also important for scientists to realize that noncoding genetic variants found in large screens, like a GWAS, could be very relevant 'hits' and that there are tools out there to help develop epigenetic models for the function of these variants."

Another University of Connecticut student, Ekneet K. Sahni, won in the category of manufacturing science and engineering for "Contact Drying in an Agitated Filter-Dryer: Experiments and Simulations." Says Sahni about the research, "Despite recent advances made towards understanding the drying phenomena, intricacies involved in the process not only due to the coupled nature of the process involving heat, mass, and momentum transport but also from their dependence on the material properties and drying conditions, do not allow quantitative predictions with extreme accuracy. The penetration model has been long known and considered as the industrial standard for contact drying. Nevertheless, it has disadvantages in the consideration of granular mechanics due to its continuous nature. Until recently, most of the DEM-based heat transfer work was either two-dimensional or in static granular beds." Sahni explains that the winning work was the first study employing 3D-DEM "to better understand the granular behavior in an agitated filter-dryer by investigating the effect of process variables on the drying performance. Major consideration has been given to the effect of speed, which has not been clearly understood in literature."

In terms of the work's relevance to future studies, Sahni says, "Along with improving our confidence for the use of DEM as an emerging tool, it fills the gap in the literature for discrete approaches. The benefits are also seen in reduced developmental resources and manufacturing costs without any production delays. Hence, process-modeling based on product development can reduce the time required to get products to market as well as the healthcare costs by saving resources. Takeaways for the scientists are that a priori performance predictive tool is developed that can help in predicting the final outcome even for the process parameters outside the range studied and for any material which gives it an edge over other designs as well as models which are mainly restricted to the parameters and/or material studied."

Brief PowerPoint presentations from each of the above graduate students appear on PharmTech.com/AAPSstudents2012. For a full list of all the AAPS 2012 Symposium Graduate Student awards, visit www.aaps.org. PT

Collaborating to Protect the Supply Chain from Counterfeiters

Adeline Siew

PharmTech speaks to Lynne Byers and Brian Johnson about Rx–360's initiatives to protect patient safety.

Lynne Byers is vice president of quality at GlaxoSmithKline.
Brian Johnson is senior director of supply-chain security at Pfizer.

Counterfeit medicines are prevalent across the globe. From proprietary medicines to generic drugs, counterfeiters are not only targeting lifestyle drugs such as Viagra and Cialis, but also expensive treatments for life-threatening conditions such as cancer. This year saw the appearance of counterfeit Avastin, which affected 19 medical practices in the United States, demonstrating that even countries with stringent regulatory and enforcement systems are not exempt from the escalating problem of counterfeits (1). In this digital age, the Internet provides an easy channel for counterfeiters to dispense their fakes. Purchasing medicines online with just a click of the mouse is becoming increasingly prevalent because of the convenience it offers, and according to the World Health Organization (WHO), constitutes more than 50% of counterfeit cases (2). In July 2011, the European Commission published the Falsified Medicines Directive (FMD) 2011/62/EU in an effort to better protect patients and consumers. The new directive, which aims to prevent falsified medicines from entering the legal supply chain and reaching patients, will come into effect in January 2013. Meanwhile, FDA's Safety and Innovation Act (FDASIA), enforced in July 2012, has made provisions to ensure the safety of drugs, for example by implementing new counterfeiting penalties, including one for trafficking fake medicines.

To examine the progress made to date in the war against counterfeits, *PharmTech* spoke with Lynne Byers, vice-president of quality at GlaxoSmithKline, and Brian Johnson, senior director of supply-chain security at Pfizer. Both are representatives and members of Rx–360, an international pharmaceutical supply chain consortium developed by volunteers from the pharmaceutical and biotech industry, with a mission to protect patient safety by enhancing the security of the pharmaceutical supply chain to assure the quality and authenticity of products and materials moving through the supply chain.

PharmTech: How successful have regulators and the pharmaceutical industry been in the battle against counterfeits?

Johnson: We have made great progress as an industry in battling counterfeit medicines and other supply-chain security breaches; however, there is still much more to do. Some examples of positive progress from a legislative perspective include the passing of the FMD in Europe and FDASIA in the US. Operation Pangea is an example of collaborative enforcement efforts, where an international law enforcement campaign involving 100 countries succeeded in shutting down more than 18,000 rogue online pharmacies. Rx–360 has also done some great work in the supply-chain security space, with several white papers that will help prevent, detect, and respond to counterfeiting and other supply-chain security threats. There are many other examples and they all contribute to our fight in different ways. Nevertheless, even with these success stories, we still see examples of global supply-chain security breaches in the news every day. We must remain vigilant.

PharmTech: What would you identify as the key provisions on the EU FMD or the US FDASIA in addressing supply-chain security? How can regulators better harmonize efforts globally?

IMAGE: HEMERA, THINKSTOCK SOURCE

Byers: In terms of improving supply-chain security, the key provisions of the FMD are as follows. All active substances, or APIs imported into the EU, will be required to be manufactured in compliance with GMP equivalent to those of the EU by Jan. 2, 2013. Written confirmation of compliance with this requirement, which will be issued by an authority in the exporting country, will need to accompany all active substances imported into the EU as of July 2, 2013. Exporting countries may apply for an exemption to these rules, but no country has been granted an exemption to date. In exceptional circumstances, and where necessary to ensure the availability of medicinal products, if the API manufacturing facility has an EU GMP certificate, then a member state may waive the requirement for written confirmation for a period not exceeding the validity of the GMP certificate. Member states that make use of the possibility of such waiver shall communicate this to the European Commission. The first country has just been granted an exemption from the written confirmation requirements—Switzerland. The process, which is to be used by each member state's regulatory authority, has not yet been communicated. In terms of regulators working more closely together, the mutual recognition of inspection reports is encouraged because this will help regulators to inspect more facilities.

Johnson: Collectively, the recent legislation in the US and EU will help enhance supply-chain security but we need similar legislative initiatives in other regions of the world to level the playing field. Our supply chains are complex and global, and because the weakest link is what criminals will exploit, global harmonization is critical. We are heading in the right direction with initiatives by regulators to collaborate on auditing, information sharing, and risk analysis. Other stakeholders are collaborating through organizations such as Pharmaceutical Cargo Security Coalition (PCSC), Pharmaceutical Security Institute (PSI), and Rx–360. It is hard to single out specific provisions of legislation, regulations, or efforts by specific organizations because they all contribute in different ways and attack different aspects of the problem. The key will be continued collaboration and avoiding working in silos, which we tend to do sometimes.

PharmTech: Could you provide an update on Rx–360's initiatives and activities thus far in 2012 and its focus of activity for 2013?

Byers: Firstly, as a consortium, we are enhancing and facilitating joint and shared audits. Both audit programs are operational following a period of piloting. Secondly, we are also addressing a broader range of supply-chain security topics. A new supply-chain security group was established and has developed and shared best practice documents. Thirdly, we are actively engaging regulators and educating legislators. In terms of communications, we have organized webinars around many Rx–360 initiatives. We have also produced 326 news flash reports and process for industry wide messaging, 90 summaries of proposed or passed regulation or legislation with an average time to publish between 6–10 days, 16 newsletters and conducted 4 open meetings.

For 2013, we have targets to increase membership in all categories and to continue to work on our priorities of the audit programs, supply-chain security and analysis, and swift dissemination of supply-chain security information.

PharmTech: To date, what are the three biggest achievements accomplished by Rx–360?

Byers: I would say that our three biggest achievements are: global collaboration between manufacturers and suppliers within the organization; a positive opinion from the Federal Trade Commission (FTC) that the audit programs, if operated as described to the FTC, are unlikely to breach US anti-trust laws; and our ability to pull together world experts to work on a problem within a tight timeframe (e.g., following the tsunami in Japan).

PharmTech: What best practices can you offer for the industry to monitor their materials coming through global supply chains, especially with products coming from emerging markets, such as China and India?

Byers: Rx–360 develops and shares best practices and points to consider in relation to the security of the supply chain. This

information is freely available on the Rx–360 website. One example of a point to consider relates to tamper evident seals, which are used on raw material containers (3).

Johnson: Companies need to have comprehensive supplier quality management programs to monitor and manage materials and products from external sources, regardless of the region being sourced from. This starts with supply chain transparency and a good understanding of all of the "players" in the supply chain. When the supply chain is well understood, companies can then use risk-assessment processes to determine appropriate strategies to mitigate risk, including risks associated with sourcing from regions with less developed regulatory infrastructure. Having clear requirements, good contracts, and robust oversight programs to ensure your suppliers meet your expectations are foundational.

PharmTech: With regards to supply-chain security, what are the common challenges faced in preventing and detecting intentional adulteration, illegal diversion, and counterfeiting of products and packaging? What steps or holistic approach is Rx–360 taking to address these problems considering how complex the pharmaceutical supply chain can be?

Johnson: As an industry, our biggest challenge and our greatest opportunity is tackling supply-chain security threats holistically. We have historically organized around individual threats, such as counterfeiting or specific parts of the supply chain, such as contract manufacturing. We also have not always balanced prevention, detection, and response to these threats. Winning this battle will require collaboration across the supply chain and between all stakeholders.

What we are trying to do in Rx–360 is to promote a holistic approach to supply-chain security. This includes defining the supply chain broadly (end to end), recognizing the advantages of working on the threats (counterfeiting, theft, diversion, and intentional adulteration) collectively, and balancing prevention, detection, and response. Our first whitepaper on comprehensive supply-chain security programs captures many of these concepts and is a good roadmap for the supply-chain security work we will be doing.

PharmTech: Could you give some background on the aims and functions of the different supply-chain working groups under Rx–360 and what each working group has achieved to date?

Johnson: Rx–360 endorsed the creation of the supply-chain security working group in October 2011. The goal of this working group was to promote a holistic approach to supply-chain security. We kicked off four working teams towards the end of 2011. The objectives for each of the teams were:

SCS Management Systems—Benchmarking and white paper describing comprehensive supply-chain security program.

Conveyance Risk Management—Benchmarking, development of risk model and white paper on using risk-based approaches to conveyance security.

Market Monitoring—Benchmarking, white paper and framework on good practices/tools-techniques, emerging technologies, to monitor the market for criminal activity.

Audits and Assessments of Third Party LSP's—Points to Consider for audits/assessments; audit standard methodology; audit tools for LSP's.

Free webinars were conducted for each workgroup and the whitepapers are currently posted on the Rx–360 website. This was all accomplished in approximately six months.

We also recently kicked off four additional workgroups with the following objectives:

Incident Management—benchmarking and development of a white paper describing a process to respond to supply-chain breaches.

Illegal Diversion—benchmarking and development of a white paper on approaches to prevent, detect, and respond to illegal diversion.

Drug Shortages—benchmarking and development of best practices for what companies can do to prevent supply-chain security breaches resulting from drug shortages.

"Serialization" Discussion Group—discussion group to share information on strategies and challenges for implementing serialization globally.

PharmTech: Could you briefly discuss best practices when it comes to responding to supply-chain security breaches?

Johnson: A centralized effective incident management process for intentional adulteration, theft, illegal diversion and counterfeits is important. A comprehensive process should have the following attributes: accurate and timely incident reporting; timely investigation; immediate actions where appropriate (e.g., notifying regulators and law enforcement); risk assessment; identifying root cause if applicable; executing corrective and preventative actions; monitoring, analysing and reviewing trends; and continuous improvement. This is not that dissimilar to the processes we use in our quality management systems.

PharmTech: The serialization implementation discussion group aims to get companies to collaborate on implementing differing requirements globally; could you discuss the challenges involved in this process and the steps being taken by Rx–360?

Johnson: First, it is important to point out what Rx–360 is not doing with this discussion group. We are not advocating on the various legislation and/or regulations being developed globally. There are other organizations actively engaged where our member companies participate so we decided to focus on an unmet need, which was to create a forum where supply-chain stakeholders could share information and approaches being taken to implement solutions and make investments (e.g., technical and IT) in a world where significantly different models are being developed. The challenges are obvious when we all work in a global marketplace.

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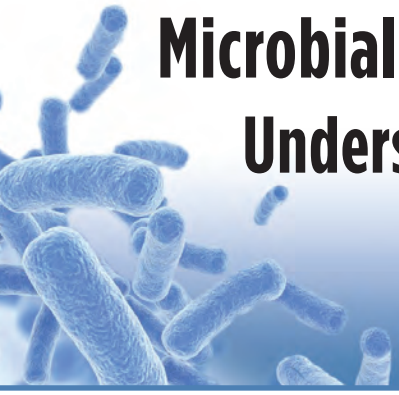

Microbial Control & Monitoring of Cleanrooms: Understanding New Regulatory Requirements

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EVENT OVERVIEW

Regulations governing cleanrooms are undergoing change. A revised US Pharmacopeia document, General Information Chapter <1116> "Microbiological Control and Monitoring of Aseptic Processing Environments," went into effect in May 2012 and focuses on ways to support microbiological control, including control of human contamination. The revised chapter <1116> references the ISO 14644 standard for cleanrooms, which replaces US Federal Standard 209E. ISO 14644 is in the process of being revised, and draft standards have been published for Parts 1 and 2, which govern classification of air cleanliness and testing and monitoring specifications. In addition, the FDA Safety and Innovation Act of 2012 is expected to affect inspections of facilities outside the US, including cleanrooms.

This webinar will focus on how the regulations have changed and what this means for cleanroom operation and monitoring. Key challenges and best practices for compliance and avoiding human contamination in drug products will be addressed.

Key Learning Objectives:

- Gain an understanding of the expectations noted in the updated USP General Information Chapter <1116>
- Learn what has changed in the ISO cleanroom standards 14644
- Learn how the FDA Safety and Innovation Act relates to cleanroom inspections
- Hear from industry experts on what steps cleanroom operators should be taking

For questions, contact Sara Barschdorf at **sbarschdorf@advanstar.com**

Who Should Attend:

- Pharmaceutical industry members involved in cleanroom operation and monitoring; QA/QC and regulatory/compendial personnel.

Speakers

Karen Ginsbury
President and CEO
PCI, Pharmaceutical Consulting Israel Ltd

Moderator:

Jennifer Markarian
Manufacturing Editor
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A Lifecycle Approach to Optimizing Cleaning Systems

Andrew Wong and Cody Shrader

Clean-in-place systems should be optimized during design and commissioning and after validation.

In the 1990s, pharmaceutical manufacturing facilities started to adopt clean-in-place (CIP) technologies to improve cleaning processes and increase critical equipment uptime. While these early systems provided significant benefits over manual cleaning, they were assembled before more modern guidance on construction and optimization. Their designs have subsequently been propagated to other production facilities without significant re-evaluation. As such, cleaning cycles are often an afterthought during current process design and development efforts, resulting in cycles that are poorly conceived, painstakingly long, or unnecessarily wasteful.

Focusing on the cleaning-system design throughout the lifecycle can yield significant cost and time savings for an organization. At the onset of a project, the equipment and piping should be reviewed for sanitary design to facilitate CIP methodology. After the design and build, cleaning cycles should be properly commissioned *via* testing and analysis. Often, the cleaning systems and cycles are qualified and validated as delivered, thus imposing change control barriers to conducting cleaning cycle optimization. Although the modification of cleaning cycles after validation is more complex, there is a pathway to measured and controlled improvements through mechanical design or automation development. This pathway requires balancing the benefits and desired outcomes of the optimization with the costs and available resources for design and implementation. The following is a brief look at techniques to optimize cleaning cycles throughout the equipment's lifecycle.

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Equipment design

An efficient cleaning cycle begins with equipment designed to ensure successful cleaning. Tank and piping design should be reviewed for sanitary cleanability, as described in section SD-3.1 of the American Society of Mechanical Engineers *Bioprocessing Equipment* standard (1). This design may include minimizing deadlegs; verifying pipes are sloped toward a drain; checking for low-point drains, sanitary connections, and valves; and verifying that all product-contact surfaces are accessible to cleaning solutions.

The next step in the cleanability review is to create a preliminary design of flow paths for CIP circuits. An example is shown in **Figure 1**. Segments of equipment and piping should be properly separated and/or combined into different cleaning circuits as part of a preliminary design. Important considerations include process and schedule requirements, potential residues, and piping design.

Process and schedule. Knowledge of the equipment's use can provide insight on process hold or transfer times. Transfer lines and tanks may need to be chained together into a single CIP circuit for quick equipment turnaround to meet these demands. Clean and dirty hold times may also affect equipment scheduling and the cleaning requirements.

Residues. Characterizing residues through cleaning studies and identifying associated product-contact surfaces aid in parameter development. Certain residues may require different cleaning solutions, concentrations, and temperatures for suitable cleaning to occur. This analysis can help organize circuits by common cleaning parameters.

Piping design. Available transfer panel connections may limit the combination of certain transfer lines and tanks. The user should account for line sizes and lengths as major pressure drops may decrease flow and turbulence within the pipe. Additional pumps and other spool pieces may be required within the system. Caution should be exercised in these cases to minimize manual configuration steps and reduce the risk of setup errors. Finally, the user should consider the availability of low-point gravity drains throughout the CIP circuit. Gravity drains remain crucial for efficient CIP cycles.

Automation-system design

The cleaning automation design also should be reviewed for efficient cleaning characteristics. Developing cycles and sequences that complement a particular automation control system greatly reduces long-term operating costs. For instance, a fast response, direct-action, process-logic controller (PLC) may minimize rinse times and water consumption by toggling through every auxiliary path on a complex bioreactor quickly enough in parallel with the sprayballs while not extending sprayball coverage test durations. In contrast, the path transition time within a distributed-control system (DCS) depends on its programming style and may require several layers of equipment module (EM) and sub-EM commands before finally reaching the target control modules (CMs). Only after waiting for valve and state confirmations can the next step begin. Here, creating a cycle that combines multiple transitions into a single grouping will result in the shortest and most cost-efficient cycle possible. Combining cleaning actions (e.g.,

rinse, drain, and air blow) within phases also reduces the cycle duration. In contrast, a strategy of using more modular, individual phases may elongate the cycle.

Various time and cost-reducing methods must be balanced with skid equipment capability. For example, one may be able to take advantage of integrated PLC capabilities of equipment (e.g., vendor-provided PLC-based centrifuges). These design considerations must be identified early in the project to ensure that quality and validation procedures can be developed to address the sampling, instrumentation, and verification requirements being built into the CIP and recipient systems.

For the CIP cycle itself, the automated step sequencing, step-transition criteria, and parameter values must be well-defined and documented to optimize utility usage while providing sufficient process control.

Sequence. Typically, a cleaning cycle should start with water rinses followed by detergent cleaning and postdetergent rinses. In between any rinse or detergent wash, the system should be drained completely to prevent dilution or chemical reaction with the next cycle step. An air-blow step, placed before the drain, can greatly decrease the gravity drain time and thus decrease the overall cycle time.

Transition criteria. Defining step transition criteria provides a way to control the critical cleaning-cycle parameters. For example, the chemical-wash duration, minimum temperature set point, and concentration target can all be set as requirements before the wash step transitions to the next step.

Parameter values. Laboratory-scale process residue cleaning studies can provide an excellent starting point for CIP cycle parameters. Scalable attributes, such as cleaning-agent concentration, process temperature, exposure time, and external energy, can be explored within the cleaning design space to isolate the most critical parameter(s). Combined with an evaluation of the most effective cleaning agent and identification of worst-case residues in the process, these laboratory-scale efforts can dramatically reduce the number of cycle iterations that must be performed during commissioning and allow for a focus on improving efficiency.

Commissioning

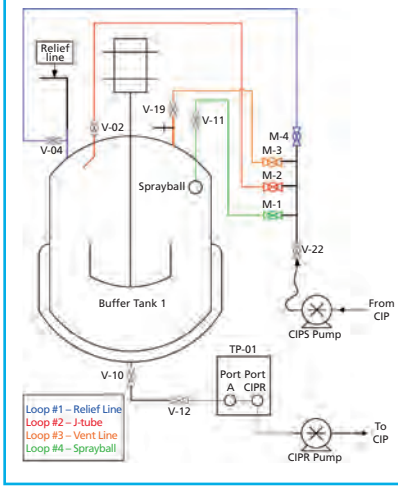
During the commissioning phase, the CIP cycle can be further optimized with hands-on development testing. Knowledge of the CIP step sequence and transition criteria are required to properly set meaningful and efficient parameters for the CIP recipes. Field verification may include monitoring drain points, viewing tank levels during recirculation, or recording pressure readings throughout the supply line.

Development testing can be aided by historical trend analysis of the test cycles. Running cycles and attempting to monitor multiple locations and parameters at the same time may be difficult with limited resources. Flow rate, pressure, temperature, conductivity, and tank-level trends, for example, can be used to optimize specific recipe parameters without having to view each instrument locally while the cycle is running. For instance, when adding chemical to a system during the recirculated wash step, the chemical must be allowed to mix evenly throughout the recirculated solution. The time required to reach the targeted steady-state conductivity can be identified by the historical trends. After comparing multiple iterations through the trends, the mixing cycle-time parameter can be set precisely based on empirical data. This method can eliminate underestimation that causes the wash recirculation to commence with nonuniform solution or overestimation that causes unnecessary cycle-time extension. These data-based decisions help maximize the efficiency of the system before validation, thus locking in cost and time gains.

Continuing optimization

After a cleaning circuit is commissioned and qualified, any changes to optimize a circuit may be difficult to implement for multiple reasons. Organizational change-control procedures may be burdensome, and the presented costs of a change may lead to skepticism from the control board. Whatever the restrictions or reservations, a case for cycle optimization can be made for poorly designed or inadequately commissioned cleaning circuits. More often than not, a call to optimize a cleaning circuit may lead to a long list of recommendations that can yield both time and cost savings.

Figure 1: An example of flow-path design.



When pursuing changes to a validated cleaning process, the user must understand the key cost drivers behind the optimization process. For instance, water consumption may be creating a situation in which captial investment in additional water-system capacity may be necessary. In this case, the optimization will save those additional capital costs. As another example, new products may require additional facility throughput. Reducing cycle time may be a simple way to boost overall facility throughput to achieve this goal. Often, investment of limited automation or capital resources into areas that do not directly impact the organization's key drivers will be rejected. Worse, implementing changes without understanding the cost drivers may result in beneficial improvements, but a failure to resolve the original problem. Additional time and resources will then be needed to further optimize a cleaning system that is still inefficient in the focus areas.

A thorough analysis and prioritization of potential changes can help identify an improvement path that all levels of management will endorse. Each change can be assessed with respect to its impact, ease, and necessity as well as other client constraints. Examples of items to consider are outlined below.

- *Cost reduction resulting from change.* What impact will the change have on the CIP utility usage, labor costs, or

FIGURE 1 IS COURTESY OF THE AUTHORS

Table I: Optimization analysis.

Change description	Cost reduction	Time reduction	Ease of change	Necessity	Other constraints	Cost of change	Sum of the categories
	0 = Low 5 = High	0 = Low 5 = High	0 = Difficult 5 = Easy	0 = Not 5 = Very	0 = Many 5 = None	0 = High 5 = Low	
Decrease air-blow time	0	3	4	2	5	5	19
Add pump-case drain	3	3	2	5	2	2	17
Combine 2 line circuits	3	5	1	2	4	1	16
Redevelop tank circuit	1	2	3	2	1	2	11

Table II: Cost-savings analysis.

Change description	Manual intervention reduction per cycle (h)	Water reduction per cycle (gal)	Number of circuits affected	Cycles per campaign	Labor cost savings ($)	Utility cost savings ($)	Total costs saved per campaign ($)
Decrease air-blow time	0	0	1	6	0	0	0
Add pump-case drain	0	120	5	4	0	24,000	24,000
Combine 2 line circuits	0.5	240	2	4	320	19,200	19,520
Redevelop tank circuit	0	10	1	2	0	200	200

Table III: Time-reduction analysis.

Change description	Cycle time decrease (s)	Manual intervention reduction (h)	Number per cycle	Number of circuits affected	Cycles per campaign	Total time saved per campaign (h)
Decrease air-blow time	40	0	7	1	6	0.5
Add pump-case drain	60	0	2	5	4	0.7
Combine 2 line circuits	1500	0.5	1	2	4	7.3
Redevelop tank circuit	600	0	1	1	2	0.3

maintenance costs? In the end, the ability to quantify the tangible cost savings can make or break a proposed project.

- *Cycle-time reduction resulting from change.* How much cycle time will be saved from parameter-value reductions or changes to procedural setup times? Cycle-time reductions should be placed in context with the overall production process to highlight the impact. This can be expressed in terms of an increase in production capacity or reduction in equipment downtime.
- *Ease of change.* How difficult will it be to implement the change? Take into account both the technical considerations as well as the impact on the existing validation.
- *Necessity of change.* How necessary is the change with regard to the cleaning cycle? Changes that improve the efficacy of the cleaning process are of primary concern.
- *Other constraints.* Are there any site, client, or other special constraints that may hinder or restrict the change? This may include additional change record documentation, agency approvals, available resources, or field accessibility.
- *Costs of the change.* What are the estimated cost implications from the change with respect to shutdown, parts and labor, and validation? These costs must be weighed against the ongoing benefit of the change.

Table I shows an example of the analysis and prioritization of potential optimizations. This semiquantitative analysis allows multiple projects to be compared based on predefined criteria for each category. In this case, each category is assigned equal weight, and a higher score indicates a more desirable project. **Tables II and III** show a more detailed analysis of the cost- and time-reduction calculations, which were translated to the ranked values in **Table I** using the pre-established criteria. Estimates of labor and utility costs are inputs for the comparison.

Conclusion

An optimal cleaning system requires effort throughout the product lifecycle. Both the mechanical and automation designs require thoughtful consideration. Optimal cleaning parameters should be explored in the laboratory design space, before scale-up and during commissioning. Once the process moves to the qualification phase, data trending and analysis should be used to establish recipe parameters. Finally, after commissioning and qualification, cycle changes and improvements should be controlled through analysis of cost, time, and resource benefits. By taking this comprehensive and holistic view, the user can truly maximize the capability and efficiency of their cleaning program.

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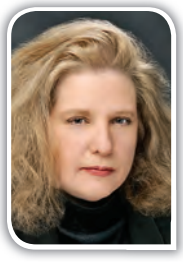
The Class of 2012 for New Molecular Entities and Biologics

Patricia Van Arnum

As 2012 comes to a close, Pfizer leads among Big Pharma companies for FDA approvals of new molecular entities and biologics.

One barometer of the health of the pharmaceutical/biopharmaceutical industry is new product development, and as 2012 comes to a close, how has the industry fared in this respect? In reviewing FDA approvals of new molecular entities (NMEs) and biologic license applications (BLAs) through Nov. 20, 2012, there are positive signs. FDA's Center for Drug Evaluation and Research (CDER) approved 31 NMEs and BLAs through Nov. 20, 2012, on par with the 30 NME and BLAs that it approved in 2011. The number of approvals, however, is not a sole determinant of success. A further look into the drug approvals for 2012 shows which companies may be graduating on the top of this year's class for new drug approvals.



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Leader of the pack

Of the 31 NMEs and BLAs approved by FDA's CDER thus far in 2012, 26 NMEs and 5 BLAs were approved (see **Table I**). Leading the large pharmaceutical companies was Pfizer, with four NME approvals. Pfizer received FDA approval for Bosulif (bosutinib monohydrate), a kinase inhibitor for treating adult patients with chronic, accelerated, or blast-phase Ph-positive chronic myelogenous leukemia. Pfizer also received approval for Elelyso (taliglucerase alfa), a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy for adults with Type 1 Gaucher disease. Pfizer partnered with Protalix Biotherapeutics in developing Elelyso with the companies forming a collaboration in 2009. Pfizer gained approval for two more NMEs: Inlyta (axitinib), a kinase inhibitor for treating advanced renal cell carcinoma, and Xeljanz (tofacitinib), a Janus kinase inhibitor for treating adults with moderately to severely active rheumatoid arthritis with whom methotrexate did not work well (see **Table I**).

Strong contenders

Six companies—Astellas, Eisai, Forest Laboratories, Roche/Genentech, Sanofi, and Teva—each had two new drug approvals thus far in 2012 (see **Table I**). Astellas had two NMEs approved in 2012: Myrbetriq (mirabegron) and Xtandi (enzalutamide). Myrbetriq is a beta-3 adrenergic agonist for treating overactive bladder. Xtandi, developed with Medivation, is an androgen receptor inhibitor for treating patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

Eisai's two NME approvals were for Belviq (lorcaserin hydrochloride) and Fycompa (perampanel). Belviq is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management. Belviq was developed by Arena Pharmaceuticals, a Zofingen, Switzerland-based company, for which it granted exclusive marketing and distribution rights to Eisai for most of North and South America. Fycompa is a noncompetitive AMPA glutamate receptor antagonist indicated as an adjunctive therapy for treating partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Forest Laboratories received approval for two NMEs in 2012: Linzess (linaclotide), developed with Ironwood Pharmaceuticals, and Tudorza Pressair (aclidinium bromide), developed with Almirall. Linzess is a guanylate cyclase-C agonist for treating irritable bowel syndrome or chronic idiopathic constipation. Tudorza Pressair is an anticholinergic indicated as a long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease.

Roche/Genentech also had two new drug approvals, one for a NME, Erivedge (vismodegib), and one for a BLA, Perjeta (pertuzumab). Erivedge is a hedgehog pathway inhibitor for treating metastatic basal-cell carcinoma or locally advanced basal-cell carcinoma that has recurred following surgery or for pateints who are not candidates for surgery or radiation. Perjeta is a HER2/neu receptor antagonist indicated in combination with trastuzumab and

docetaxel for treating patients with HER2-positive metastatic breast cancer.

Sanofi received approval for its NME Aubagio (teriflunomide) and its BLA Zaltrap (ziv-aflibercept). Aubagio is a pyrimidine synthesis inhibitor for treating patients with relapsing forms of multiple sclerosis. Zaltrap is a recombinant fusion protein, which acts as a soluble receptor that binds to vascular endothelial growth factor-A (VEGF-A), VEGF-B, and placental growth factor and is used to treat metastatic colorectal cancer. Sanofi partnered with the biopharmaceutical company Regeneron Pharmaceuticals for Zaltrap.

The generic-drug company Teva had two approvals, one for its NME Synribo (omacetaxine mepesuccinate), a drug to treat leukemia, and a BLA for tbo-filgrastim, which was approved as an original BLA and not as a biosimiliar to Amgen's Neupogen (filgrastim), which is a previously approved biologic. Tbo-filgrastim is a human granulocyte colony-stimulating factor produced by recombinant DNA technology for reducing neutropenia in patients with non-myeloid malignancies.

Other companies

Approvals constitute a mixed bag for other large companies. Merck & Co. gained one new drug approval in 2012 for Zioptan (tafluprost ophthalmic solution), a prostaglandin analog indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Bayer received FDA approval for Stivarga (regorafenib), a kinase inhibitor for treating metastatic colorectal cancer. Eli Lilly's subsidiary Avid Radiopharmaceuticals received approval for the radioactive diagnostic agent, Amyvid (florbetapir F-18). Takeda Pharmaceutical and Affymax received approval for Omontys (peginesatide acetate), an erythropoiesis-stimulating agent to treat anemia.

Equally important in evaluating R&D productivity is seeing which companies did not receive FDA approval for NMEs or new biologics (excluding vaccines). Through Nov. 20, 2012, GlaxoSmithKline, Novartis, AstraZeneca, Bristol-Myers Squibb, and Abbott were among the large companies without a NME or original BLA FDA approval this year. As the industry waits for 2012 to come to a close, it has yet to be seen if their late-stage candidates under review will get the FDA nod this year. **PT**

Table I: FDA approvals of new molecular entities (NME) and biologic license applications (BLA) in 2012.*

Company	Proprietary name (active ingredient)	Dosage form (route)
Affymax; Takeda Pharmaceutical	Omontys (peginesatide acetate); NME	Solution (intravenous, subcutaneous):
Amarin Pharmaceuticals	Vascepa (icosapent ethyl); NME	Capsule (oral)
Astellas	Myrbetriq (mirabegron); NME	Tablet, extended-release (oral)
Astellas	Xtandi (enzalutamide); NME	Capsule (oral)
Avid Radiopharmaceuticals	Amyvid (florbetapir F-18): NME	Solution (intravenous)
Bayer Healthcare	Stivarga (regorafenib); NME	Tablet (oral)
BTG International	Voraxaze (glucarpidase); BLA	Injectable (injection)
Discovery Laboratories	Surfaxin (lucinactant); NME	Suspension (intratracheal)
Eisai	Belviq (lorcaserin hydrochloride); NME	Tablet (oral)
Eisai	Fycompa (perampanel); NME	Tablet (oral)
Ferring Pharmaceuticals	Prepopik (citric acid; magnesium oxide; sodium picosulfate); NME	Solution (oral)
Forest Laboratories	Linzess (linaclotide); NME	Capsule (oral)
Forest Laboratories	Tudorza Pressair (aclidinium bromide); NME	Powder, metered (inhalation)
Gilead Sciences	Stribild (cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate); NME	Tablet (oral)
Leo Pharma	Picato (ingenol mebutate); NME	Gel (topical)
Mayo Clinic PET Radiochemistry Facility	Choline C-11; NME	Injectable (intravenous)
Merck & Co.	Zioptan (tafluprost); NME	Solution/drops (ophthalmic)
Onyx Pharmaceuticals	Kyprolis (carfilzomib)	Powder (intravenous)
Pfizer	Bosulif (bosutinib monohydrate); NME	Tablet (oral)
Pfizer	Elelyso (taliglucerase alfa); NME	Powder (intravenous, infusion)
Pfizer	Inlyta (axitinib); NME	Tablet (oral)
Pfizer	Xeljanz (tofacitinib); NME	Tablet (oral)
Roche/Genentech	Erivedge (vismodegib); NME	Capsule (oral)
Roche/Genentech	Perjeta (pertuzumab); BLA	Vial (single-use)
Sanofi	Aubagio (teriflunomide); NME	Tablet (oral)
Sanofi	Zaltrap (ziv-aflibercept); BLA	Injectable (injection)
Teva	Synribo (omacetaxine mepesuccinate); NME	Powder (subcutaneous)
Teva	Tbo-filgrastim; BLA	Injectable (injection)
Thrombogenics	Jetrea (ocriplasmin)	Injectable (intravitreal)
Vertex Pharmaceuticals	Kalydeco (ivacaftor); NME	Tablet (oral)
Vivus	Stendra (avanafil); NME	Tablet (oral)

* Source: FDA's Center for Drug Evaluation and Research and Drugs@FDA; FDA approvals as of Nov. 20, 2012. Avid Radiopharmaceuticals is a subsidiary of Eli Lilly. Takeda/Affymax's Omontys and Omontys-Preservative Free both approved as new molecular entities. Teva's TBO-filgrastim received approval as an original BLA.

Development and Commercialization of a Novel Modified-Release Tablet Technology

Kevin D. Altria and James Taylor

ISTOCKPHOTO/THINKSTOCK IMAGES

GlaxoSmithKline recently developed a novel technology for the formulation of modified-release tablets. Commercialized as DiffCORE, the technology combines the use of apertures that are mechanically drilled into functional film-coated tablets, with traditional polymer matrices that control the mechanism of core erosion and diffusion. The authors describe the route from development to commercialization of this modified-release approach.

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Submitted: Feb. 15, 2012. Accepted: Mar 15, 2012.

Dedication
This article is dedicated to the memory of Dr. John Hempenstall who greatly supported the development and commercialization of this technology. John was a great friend and mentor to many GSK colleagues.

There are a number of approaches to developing a modified-release (MR) formulation, which include traditional polymer matrices, such as a hypromellose matrix (1), and more complex multilayered matrices with or without additional functional excipients (2). There are benefits and restrictions to every approach, which include technology requirements, and applicability to drug type/concentration range. A new MR approach has recently been developed and commercialized by GlaxoSmithKline (GSK) under the trade name of DiffCORE. This article describes the MR approach, its *in vivo, in vitro,* and industrial commercial performance, and potential benefits of the approach.

What is the background to the MR approach and its technological development?

The approach involves using mechanical drilling of functional film-coated tablets (see **Figure 1**) to form apertures of known size and position in the film coat. The release rate of the drug can be modified and controlled through altering the exposed surface area and the composition of the tablet core. The manufacture of the tablets utilizes standard manufacturing unit operations (i.e., blending, granulation, and compression). The core formulation and the manufacturing process impact the performance of the final product as it would on any traditional solid dose.

GSK purchased an original patent in 1993, which used a film coating based upon ethylcellulose. While this film coating was a semipermeable coating, when used in the DiffCORE process, it behaves essentially as an impermeable barrier. The coating retards the release of the API from the majority of the core surface area. The apertures in the coating maintain the release rate of the API from the core throughout the entire gastrointestinal tract. This approach was found to be suitable for compounds which had high solubility, primarily weak acids. Weak bases, which at that time formed a large part of the MR portfolio, were found to exhibit reduced release on leaving the gastric environment due to the pH-driven reduction in solubility and thereby availability.

Using targeted experiments, a new film coating system was developed, which enabled the technology for use with weak bases (3). The increase in potential products that could

benefit from the new film-coating system prompted further investment of time and resources to fully explore the capabilities of this technology.

The new coating system developed was an enteric film coat based upon previous research into different detackifiers. For weak bases, this coating initially retards the release of the active material to the drilled apertures while within the high-solubility gastric environment. Upon reaching the higher pH of the intestines, the coating dissociates and becomes soluble. The dissolution of the coat increases the exposed surface area of the core, which increases the availability of the exposed drug substance, thereby compensating for the decreased solubility. By making use of established polymer matrix techniques, the core is formulated to ensure a controlled release rate is maintained.

Further refinements have been made for specific compounds, dependant on the product's pharmacodynamics. The use of a bilayer core enables the combination of an immediate-release (IR) layer and a MR layer. The IR layer reduces the time to reach the minimum therapeutic dose for the patient while the MR layer provides a maintenance dose. This bilayer approach can obviously be extended to combination products though this has not been trialled at this time (4). GSK has several products utilizing this technology under development at various clinical stages, with Lamictal XR (lamotrigine) being the first product commercially available on the market.

How did the technology become commercialized?

There were several aspects that required alignment for this technology to mature. The most fundamental was the initial drive or need to use a technology. Without this, there was little interest in investing potentially large sums of money with the risk of no return. The second was having compounds to work on, otherwise the resources associated with the technology are not just non-value adding but costly in a budget constrained environment. Using development compounds, by necessity, to drive a technology development ties the two processes intimately together in terms of risk—both the chance of the process not being technically deliverable for specific milestones, and the potential for a compound not progressing reducing the commitment on the technology side. The final aspect was that there was a clear strategic intent on developing commercial platforms that delivered rapid development on a wide range of active compounds.

This technology was well-placed with regards to commercialization as there was a genuine need, strong sponsorship, and was simple to apply in development. The ability to manually drill apertures on low numbers of tablets or caplets allowed for very quick *in vitro* proof of concept (PoC), typically under a week including analysis, enabling rapid development programs.

Once PoC had been proven, the technology program accelerated in line with the compound. Having a manual low-volume manufacturing method does not enable a technology to be used to manufacture clinical supplies for Phase IIb or Phase III, let alone commercial production. Therefore, post PoC development, a prototype automated machine had to be proven and validated at the same pace as the compound needs.

Figure 1: Film-coated tablets with apertures of known size, 2 mm (blue), 3 mm (brown), and 4mm (green).

The final and perhaps the most costly step in establishing a commercial technology was to develop the prototype into a true manufacturing process (equipment, facility, and ways of working) with the full support of the commercial organization. The ability to complete the development process on a commercial scale at a manufacturing site requires great organization and cooperation between the development and manufacturing teams as both are working against aggressive timelines. The requirements for establishing a new technology from a business and industry perspective were broad, and encompassed well-documented validation and regulatory requirements. As this was a novel technology, education of external parties, such as FDA, was required to increase understanding of the technology to enable appropriate assessment of the control measures. This whole process enabled GSK to cover the entire gamut of scales in manufacturing with the benefit of having a scale-independent technology from development to commercialization.

Isn't this just a modified osmotic pump?

At first glance, this MR approach has some similarity to osmotic pump tablets (5) in that they both have apertures in their coatings, but the aperture sizes are significantly larger in this approach with an aperture on each face of the tablet (6). The larger apertures ensure that no hydrostatic pressures build up, and that release is controlled by the exposed surface area, which is typical of polymer systems, and not osmotic pumps (7).

There are two main control mechanisms:

- Polymer type and concentration, which dictate the erosion rate of the tablet core and subsequent diffusion rate of the API.
- The surface area of the core exposed for release of the API, which is controlled by (a) the aperture size in the gastric region, and by (b) the core geometry in the intestinal region.

ALL FIGURES ARE COURTESY FROM THE AUTHORS.

Figure 2: *In vitro* dissolution data of a single input batch varying in aperture sizes. The drug product was exposed to pH 1.2 media during the first two hours, followed by pH 6.8 media for the remaining six hours.

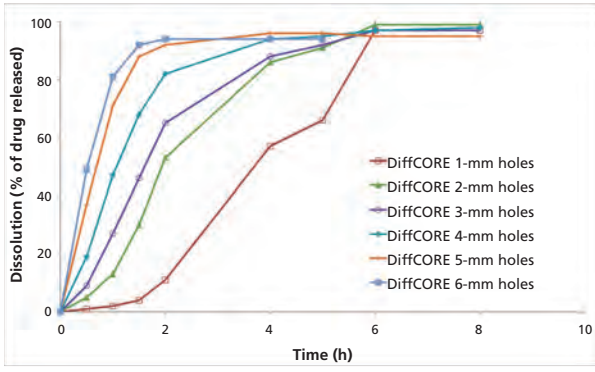
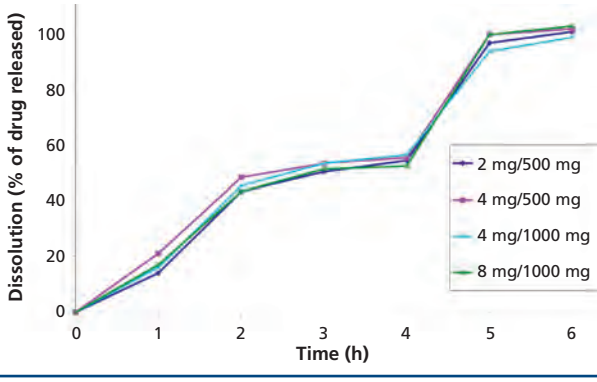


Figure 3: Varying aperture sizes allows for consistent product performance for a range of different doses on a combination product.



What API types and doses can the approach be used for?

Due to the nature of this technology, there has been a perceived level of risk associated with "being the first" so the initial uptake has been with compounds that have had a number of challenges or difficulties in developing a more traditional MR dose form. However, in summary, a range of compounds across the Biopharmaceutics Classification System (BCS) have been tested and shown great success. More recently, the launch of a commercial product has helped to reduce this perceived risk and embed the technology within GSK.

Three late-phase compounds have shown the breadth of the technology. Two products utilized doses as low as 2 mg, and have proven to be consistent and reproducible in their delivery while a high-dose product, at 1000 mg, has been kept to a single daily tablet to aid patient compliance without having to use unnecessary levels of polymers.

How is the release rate modified and controlled?

This novel technology uses the combination of apertures in functional film coatings with traditional polymer matrices. Unlike typical polymer matrices, these formulations use a low-viscosity polymer to control the mechanism of core erosion and diffusion. The low-viscosity polymers are more suitable because the hydration of the polymer is constrained by the film coating in the gastric environment so there is little erosion occurring prior to the gel-structure formation.

The ability to combine these matrices with a functional film coating also provides dual control mechanisms conferring several advantages. Difficult or distinct release rates can be achieved, which show little food effect; the patient is doubly protected by the control mechanisms, reducing the risk of dose dumping; a single batch of tablets can be used to develop a suite of release rates simply by modifying the exposed core surface area, as shown in **Figure 2.**

During the first few hours when the functional coating is insoluble in the acidic environment, the exposed surface area is the dominant control mechanism, and the release rate is controlled by the size of the apertures. As the exposed surface area increases, the core formulation shows increasing influence on the release rate. Once the aperture size is large enough, the core formulation and API characteristics become dominant in controlling the release. A high-dose, soluble drug is used in this example to demonstrate this effect. After four hours, when the drug product is exposed to media at pH 6.8, the functional coating becomes soluble, and the core characteristics drive the rate of release.

Throughout the development process, a range of doses will often need to be developed to identify the most appropriate dose to treat varying degrees of patient condition or simply for dose titration. When designing combination products, large numbers of dose combinations can make development programs somewhat complex.

The data in **Figure 3** show a product covering four doses across two APIs. Using platform granulations and varying only the aperture sizes, doses were designed to have overlaying profiles.

How is a formulation designed to obtain a clinical outcome using this approach?

The formulation is developed based upon defining the physiological, pharmacodynamic, and pharmacokinetic (PK) data as a clinical requirement. Once the solubility profile and PK target is clear with key requirements (i.e., area under the curve [AUC] and maximum concentration achieved [Cmax]) the appropriate release rate and *in vitro* profile for the finished product can be established. The ability to use a selection of proven product types, for example bilayer DiffCORE, or multiple release profiles from a single batch allows rapid product manufacture for clinical testing against the defined target profile(s).

One of the benefits associated with DiffCORE has been the reduction in the number of clinical trials for formulation evaluation. Each clinical trial is costly to resource in terms of equipment, materials, planning, and patient recruitment. A review of six compounds that have used the DiffCORE technology showed that half required a single visit to the clinic to define the formulation for final development (see **Table I**). It also showed that the technology enabled development of a suitable formulation for compounds that were historically difficult to develop as MR products.

Table I: Number of formulations evaluated in clinical studies with and without DiffCORE (GlaxoSmithKline).

Molecule	Clinical studies pre DiffCORE	Number of formulations	Clinical studies DiffCORE	Number of formulations
Lamictal XR	0	NA	1	3
GSK1	5	20	3	11*
GSK2	4	27	3	15*
GSK3	0	NA	2	2
GSK4 /Metformin	0	NA	1	6
GSK5	0	NA	1	4*

*DiffCORE plus other modified-release formulations.
DiffCORE is GlaxoSmithKline's proprietary modified-release, drug-delivery technology.
NA = not applicable

What controls do you need over the apertures?

GSK identified four potential quality attributes throughout the development lifecycle to ensure consistent and robust performance of the product: presence, size, position, and depth of the apertures.

The effect these have on the performance of the product are dependent on the API and core formulation. Those products with greater robustness are evidenced by a wide tolerance of the aperture size (± 1 mm) with little impact of aperture position and depth, which provides a broad manufacturing control strategy using generic process controls. Those products that require more rigorous process controls around the aperture formation will require a unique process recipe, for instance, a high sensitivity to aperture depth, ± 10 μm, would require specific drill movement parameters to ensure precise aperture formation. Typical process controls maintain the aperture size within ± 0.2 mm, the position to within 0.3 mm and the depth to within 50 μm of target.

The online inspection systems, visual imaging, and laser displacement, measure every aperture formed in terms of size, position, and depth. The recipe-controlled specifications are used to categorize the product as acceptable or non-acceptable. Products that do not meet the specification are automatically removed from the process flow with a confirmation of removal. During routine production, the current process efficiencies are being measured at greater than 99.9%.

Does the drilling process affect uniformity or stability?

For the products developed to date, GSK typically observed no change in release profile on stability for the drilled products. **Figure 4** shows stability dissolution performance of one product over 56 months with no discernible difference indicating very good stability and reproducibility. Since the drilling process only exposes a small surface area of the product while the remainder is coated with a reduced permeability enteric film coating, the shelf life does not appear to be, nor is expected to be, any different to a cosmetically film coated product.

Figure 4: Dissolution performance of the initial product and after 56 months storage at 30 °C/65 % relative humidity (RH).

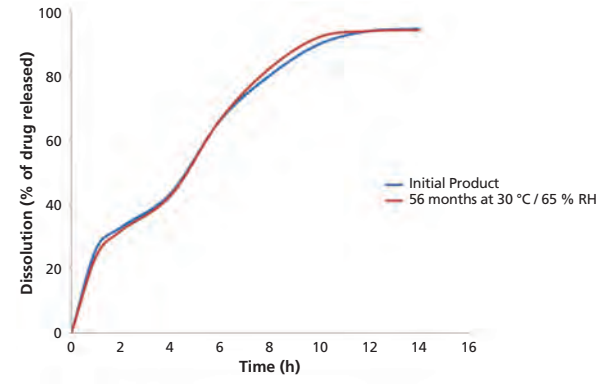


Figure 5: Development equipment with on-line inspection systems.

Dedusting and metal checking are used as part of manufacturing, similarly to compression, reducing potential operator exposure and contamination downstream. The potential for product damage on downstream processing, such as packaging, was investigated showing that, using typical equipment, the process was optimized to eliminate potential defects.

How do you scale up the process for commercial production?

Post PoC, a development machine has been purpose built to manufacture these products (see **Figure 5**). This machine will manufacture up to 10,000 units per hour with online inspection of the product quality attributes impacting performance.

For commercial production, GSK uses machines that are currently installed in its global manufacturing facility in

contin. on page 54

JONATHAN EVANS/PHOTODISC/GETTY IMAGES

PharmTech.com/outsource

Acquisitions Reshape the Bio/Pharm Services Industry

Jim Miller

The quest to build critical mass and broaden capabilities has been a key factor in deal-making.

The year 2012 has been an important year for acquisitions in the bio/pharmaceutical CMC (chemistry, manufacturing, and controls) contract services industry. Some of the premier names in the industry have been involved in major deals, either as buyers or sellers. The pace and nature of these deals suggests that there are more to come in the next several years.

PharmSource has counted at least 20 acquisitions of CMC service providers in 2012 through the end of November 2012 (see **Table I**). Some of the larger and more significant deals are listed in the accompanying table. There seem to be a wide variety of underlying drivers for the acquisition activity, but several really stand out.

Table I: Select mergers and acquisitions in the contract-services industry, 2012*

Buyer	Target	Target capabilities
Patheon	Banner PharmaCaps	Dose manufacturing: softgels
Aenova	Temmler Group	Dose manufacturing: solid, semisolid, liquid
Siegfried	AMP	Dose manufacturing: injectables, sterile liquids
CMC Biologics	Xoma manufacturing facility	Biologic API
Sigma Aldrich	BioReliance	Analytical testing
Catalent	Aptuit clinical packaging business	Clinical supplies and packaging
United Drug/Sharp	Bilcare Clinical Supplies	Clinical supplies and packaging
BC Partners	Aenova	Dose manufacturing: softgels and solids
Mayne Pharma	Metrics	Clinical supplies and analytical testing; generic products
Renaissance Pharma	DPT Laboratories	Dose manufacturing: semisolid, liquid, injectable

* Acquisitions as of November 2012.
CMC is chemistry, manufacturing, and controls.
Source: PharmSource

Size matters

Arguably, the most important of these drivers has been the pursuit of large size. Company size and breadth of capabilities has clearly been a major criterion in the awarding of strategic sourcing relationships for clinical research services by global bio/pharmaceutical companies. Size reflects broad scope, financial strength, and the ability to achieve economies of scale. Although the strategic sourcing trend is still evolving in manufacturing, where CMOs are battling with in-house capacity, it has penetrated the clinical packaging and analytical services segments of CMC services, where large companies are clearly favored.

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Another advantage of size is that larger companies get the attention of the investor community, which provides investment capital for growth and the opportunity for current owners to realize the value of their investments. Whether the plan is to eventually sell equity to the public, or sell to another private equity firm, the size of a company is important to the investment community, which likes to put large amounts of capital to work in any given deal. Even if a CRO or CMO is a business unit of a larger, diversified company, size is likely to be critical to getting senior management attention and access to corporate capital for investment.

Broader capabilities

Another driver of acquisition activity in 2012 has been the desire of companies to position themselves in segments of the market that promise more robust growth or better margins than more mundane services. Highly desirable opportunities have included services that support development and manufacture of biopharmaceuticals (both APIs and injectable drug products) and drug-delivery technologies that can be broadly applied such as softgels. Examples of deals driven by these considerations include the acquisitions of Banner PharmaCaps and Aenova, both of which are major players in the softgel business, and Sigma Aldrich's acquisition of BioReliance, a market leader in services for development of biologics.

When the objective is to add important capabilities in critical markets, deals can be strategically important even if they are not large. So-called "bolt-on" acquisitions enable CMOs and CROs to add skills and facilities quickly and with immediate payback and are not disruptive to the acquirer's core operations. A recent example is the acquisition of the UK biosafety laboratory Vitrology by SGS Life Sciences, which extended SGS's offerings for the testing of biopharmaceuticals.

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A third rationale that has underlain several recent acquisitions has little to do with contract services. CMOs are being acquired to serve as platforms for building generic products businesses. DPT Laboratories, Confab, and Metrics have all been acquired by companies whose ultimate objective is to build a generic or specialty pharmaceutical business by pairing acquired manufacturing capacity with in-licensed or acquired products. Those companies, well-respected in their respective service areas (semisolids and liquids for DPT and Confab, solid dose and analytical for Metrics), will maintain their successful contract services businesses but also will take on more production of proprietary products.

More to come

Despite, or even thanks to, the recent turmoil in the world economy, we expect to see more acquisitions of CMC service providers in the near future. Not only are there clear rationales for making acquisitions of CMC companies, but there also seems to be plenty of resources available to do them. Many private-equity firms are capable of financing these deals, and they especially like the opportunity to consolidate highly fragmented industries, such as CMC development and manufacturing services. Banks in North America, even some European banks, are eager to help fund these deals in an environment where overall loan demand is depressed.

More acquisitions of CMC service providers are expected in the near future.

The CMC services industry, especially contract manufacturing, will benefit from having a core of large global companies capable of serving global bio/pharmaceutical companies. Catalent, which was assembled through acquisitions, has already topped the $1 billion mark, and Patheon has gotten there with the Banner acquisition. Aenova and Aesica, both based in Europe, have stated their intention of getting to the $1 billion mark, and Aenova is more than halfway there after its Temmler acquisition.

Acquisitions will continue to reshape the CMC services industry, and they are a sign that the industry is reaching a new level of maturity. **PT**

Formulation – *contin. from page 51*

North Carolina (see **Figure 6**). These machines have the same functionality and process parameters as the small-scale equipment, thereby eliminating scale-up and increasing output (approximately 120,000 units per hour). The process is scale-independent, and the final development process is transferred directly to the commercial machines. The current manufacturing process exhibits consistent content uniformity with good variability (mean = 99%, standard deviation = 0.82, based on 14 commercial batches).

What are the advantages and limitations of this MR approach compared with other approaches?

Development of modified release products can be a costly activity, which may involve several clinical studies and formulation activities before a desired PK profile is obtained. There are several enabling features of this MR approach that minimizes these costs:

Advantages

- Rapid development of multiple release rates/profiles
- Reduction of costs associated with changes to clinical requirements
- Production of common release profiles within a product range
- Accommodates combination products
- Simple manufacturing techniques
- Elimination of technical transfer for aperture formation process
- Full inline inspection of the quality attributes at the point of manufacture.

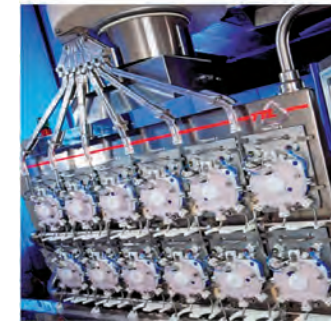
Disadvantages

- An extra process during manufacturing is required
- Specific novel equipment must be used
- Manufacturing capacity is typically approximately 120,000 units per hour.

Conclusion

Technology development can be a risky process for a business and seems to be increasingly left to academia to prove the principles and prototype. The success of this technology within GSK shows that this need not always be the case. A small investment in targeted work can lead to advances that benefit the business as well as the patient, provided that relevant risk/benefits are monitored at all stages of the process.

Figure 6: Commercial manufacturing equipment with online inspection systems.



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Catalent Announces Cell-Line Sales Agreement With Cevec

Catalent Pharma Solutions has entered into a commercial cell-line sales agreement with Cevec Pharmaceuticals for recombinant human alpha-1 antitrypsin. The companies have also signed a joint development and marketing agreement that combines Cevec's Cap cell line, a high performance protein expression platform originally derived from primary human amniocytes and Catalent's GPEx technology, a gene-insertion method providing single-copy gene integration at multiple genomic locations in dividing cells. The agreement will enable the copromotion of the combined technologies to biotechnology companies needing cell-line development and manufacturing of various proteins.

USP Selects Thermo Fisher Scientific for Spectral Library Development Project

The United States Pharmacopeial Convention (USP) has selected Thermo Fisher Scientific's TruScan RM and microPHAZIR RX instruments to support its recent initiative to provide USP-approved libraries to pharmaceutical manufacturers. The spectral library project is one of the many USP initiatives designed to set standards that help ensure the quality, safety, and benefit of medicines and foods. The project aims to provide manufacturers with a USP-approved library of methods for use across the globe for material identification. It is intended to provide a harmonized approach to ensuring the quality of pharmaceutical ingredients before entering the supply chain.

"With increases in supply-chain variability, the development and deployment of public standards is critical to ensure the safety and efficacy of medicines," said Edward Zhao, vice-president, business development of USP, in a Thermo Fisher press release. "USP relies on advanced analytical capabilities and modern equipment, such as the TruScan RM and microPHAZIR RX, to provide the highest quality of standards for use by global pharmaceutical manufacturers."

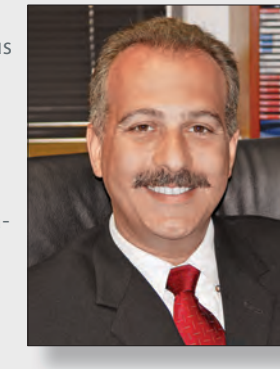
TruScan RM, a Raman-based spectrometer, and microPHAXIR RX, based on near-infrared, will be used to develop all methods included in the USP spectral library. Both instruments are designed to enhance user-friendly operation and enable on-the-spot, actionable pass–fail results within seconds.

Neptune Provides Update on Production Plant

Neptune Technologies & Bioressources, a manufacturer of phospholipid products for the nutraceutical and pharmaceutical industries, reported that, on Nov. 8, 2012, an explosion and fire destroyed its production plant located in Sherbrooke, Quebec, Canada. Three employees were fatally injured. Eighteen other people were transported to the hospital—four of whom were severely injured. The incident completely destroyed Neptune's current production plant that was in operation in Sherbrooke, but damages at the expansion facility currently under construction adjacent to Neptune's Sherbrooke plant appear to be limited, according to the company. Neptune is strategizing on an action plan going forward to allow it to resume production and meet client demands, and plan particulars will be announced at a later date.

Q&A with

Richard Shor, *President of SaniSure*



PharmTech:
How has the increasing focus on biopharmaceuticals affected your business?

Shor:
In the sense that biopharmaceuticals are now a growth industry as opposed to the traditional chemical–pharmaceutical industry, it has impacted us greatly. Single-use process components are ideal for the biopharmaceutical arena. Batches are typically smaller and most of the processes are not using chemicals that will affect the components we provide.

PharmTech:
How will the industry remain innovative as it reduces spending on research?

Shor:
We have not seen any decline in innovations; however, it is now coming from other sources. What we are seeing is the partnership and licensing of a molecule to a start-up or small biotechnology company. This model allows the big companies to reduce their R&D budgets and risk exposure while allowing the smaller companies to get funding through private equity or other sources. If the product is a success, the investors win as well as the large biotechnology companies that will purchase the smaller company in the end.

PharmTech:
Do you see a new industry trend emerging?

Shor:
Regulatory compliance has become a big part of our customers' requirements. Biotechnology companies are demanding much tighter control and assurance of our products. As a supplier of single-use components and systems, SaniSure is now being asked to have control of our supplier base and the raw materials they are using. The onus is on us to assure a consistent and stable level of quality and control.

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Meissner's QuaDrum storage containers are available in 50-, 100-, and 200-L volumes to support its One-Touch single-use biocontainer assembly portfolios. The polyethylene storage containers are chemically resistant and easy to clean, and are available with slotted or solid lid options to offer varying levels of accessibility. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Digital microscope

Natoli's digital microscope captures photos and video, records measurements, and provides tablet- and tooling-inspection applications. The versatile, compact device is CE certified and fully customizable with a collection of optional accessories.
Natoli Engineering Company, *St. Charles, MO • www.natoli.com • tel. 636.926.8900*

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Fette Compacting America's FE55 tablet press is equipped to handle 90% of common tablet formats. The FE55 can produce single- and double-layer tablets and perform direct pressing. The unit features punch stations that allow for a 50% output increase. **Fette Compacting America,** *Rockaway, NJ • www.fetteamerica.com • tel. 973.586.8722*

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Weiler Engineering, *Elgin, IL • www.weilerengineering.com • tel. 847.697.4900*

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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*

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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*

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Viewpoint – *contin. from page 62*

manufacture, use, or sale of drugs regardless of whether the activity occurs pre- or postapproval (11).

The decision has major consequences for the industry. If the Hatch–Waxman Act protects postapproval batch testing, the value of patents on analytical methods, particularly covering biosimilars, may significantly decrease.

Chief Judge Rader, who authored the majority opinion in *Classen*, issued a lengthy and sharply worded dissent in *Momenta*, criticizing his fellow judges for failing to follow *Classen* (12). Judge Moore, who authored the majority opinion in *Momenta* and a dissent in *Classen*, saw it differently. She squared the *Classen* and *Momenta* decisions noting that, in *Classen*, there was no requirement that Biogen or GSK submit any data to FDA. By contrast in *Momenta*, FDA required analytical records for each batch of enoxoparin produced in order to maintain regulatory approval (13).

The Supreme Court could very well end up resolving the issue.

Whether one can reconcile these two decisions, the Supreme Court could very well end up resolving the issue. GSK filed a petition for certiorari asking the Supreme Court to clarify "[w]hether the Federal Circuit's interpretation of § 271(e)(1) [in *Classen*], which arbitrarily restricts the safe harbor to preapproval activities, is faithful to statutory text that contains no such limitation, and decisions of this Court rejecting similar efforts to impose extratextual limitations on the statute" (14). The Supreme Court may welcome the opportunity to provide its guidance on the scope of Hatch–Waxman's safe harbor—an issue the high court has addressed twice before (15)—especially in light of this seeming inconsistency in Federal Circuit precedent in this area of the law.

References

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2. 35 U.S.C. § 271(e)(1) (2012).
3. 659 F.3d 1057, 1060, 1070 (Fed. Cir. 2011).
4. Ibid. at 1060.
5. Ibid. at 1070-72.
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7. 686 F.3d 1348 (Fed. Cir. 2012).
8. Ibid. at 1351.
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10. Ibid. at 1352-53.
11. Ibid. at 1354-55.
12. Ibid. at 1361-76.
13. Ibid. at 1357-58.
14. Petition for a Writ of Certiorari at i., GlaxoSmithKline v. Classen Immunotherapies, Inc., No. 11-1078 (U.S. Feb. 28, 2012).
15. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 206-07 (2005); Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990). **PT**

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Patents and Postapproval Batch Testing

Kevin Murphy and Andrew Nason

Can postapproval FDA filings immunize pharma companies from patent lawsuits?

FDA requires that pharmaceutical companies create and maintain pre-approval batch records for both generic and brand drugs. In general, a company can do so without risking infringing any patents covering manufacture of a drug. Congress enacted the so-called "safe harbor" provision of the Hatch–Waxman Act in 1984 specifically allowing pharmaceutical companies to test their products prior to obtaining regulatory approval to market them (1). Under that provision:

> *It shall not be an act of infringement to make, use, offer to sell, or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biologic products (2).*

But what happens if the company is sued for infringement after it obtains approval from FDA? Until recently, most in the legal industry would have said that postapproval batch testing is not protected by Hatch–Waxman. As recent as 2011, in *Classen Immunotherapies, Inc. v. Biogen IDEC*, the Federal Circuit Court of Appeals—the final authority on most patent matters—decided that the safe harbor does not apply to "information that may be routinely reported to the FDA, long after marketing approval has been obtained" (2). Classen had accused Biogen and GlaxoSmithKline (GSK) of infringing Classen's patent relating to an immunization method (3). The patented method involved screening immunization schedules and selecting and administering the schedule that presented the lowest risk of developing certain immune-mediated chronic disorders later in life (4). As part of an FDA study, Biogen and GSK used the patented methods to provide vaccines, advise on immunization schedules, and report adverse vaccine effects to FDA (5). Biogen and GSK contended that their activity fell within the safe harbor (6). But the Federal Circuit disagreed, concluding that the provision only provides a safe harbor to expedite the development of information for regulatory approval of generic counterparts of patented products. GSK and Biogen were held not immune from Classen's suit.

If the Hatch–Waxman Act protects postapproval batch testing, the value of patents on analytical methods, particularly covering biosimilars, may significantly decrease.

But in August 2012, the same court decided in *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, (7) that the safe harbor provision indeed might immunize postapproval activities. The patent at issue in *Momenta* covered a method for analyzing batches of enoxaparin, a synthetic version of the blood-thinning agent heparin (8). Because of enoxaparin's unique chemical makeup, FDA requires batch analysis as a condition for the post-FDA approval sale of the drug (9). Momenta claimed that Amphastar's quality control testing of its enoxoparin batches infringed Momenta's patent; Amphastar argued that its testing fell within Hatch–Waxman's safe harbor because FDA required the testing (10). The Federal Circuit determined that § 271(e)(1) unambiguously covers any activity reasonably related to developing and submitting information under a federal law that regulates the

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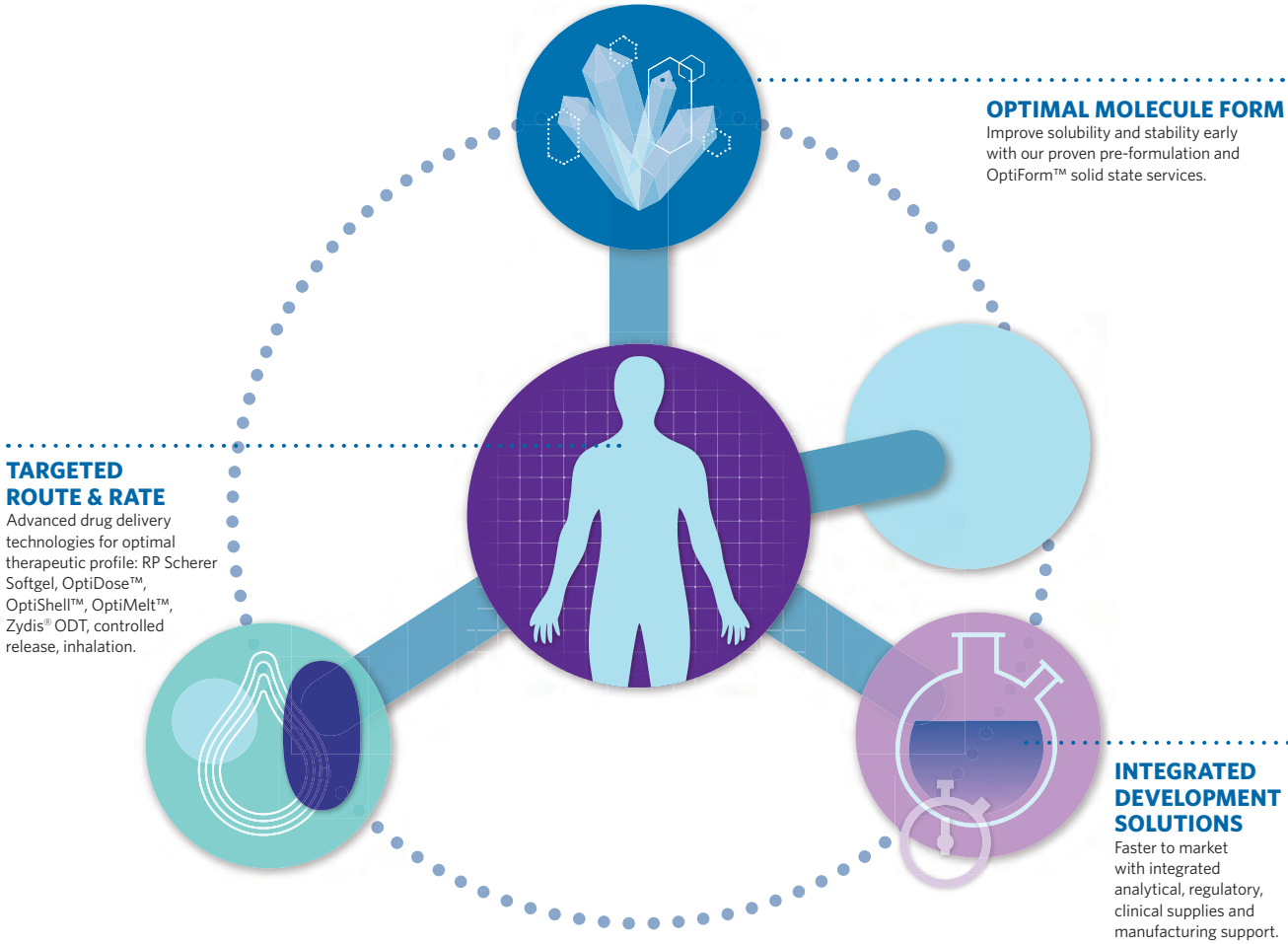

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