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PLUS: Counterfeit Detection Techniques : Improving API Synthesis : Functional Equivalence for Equipment Replacements

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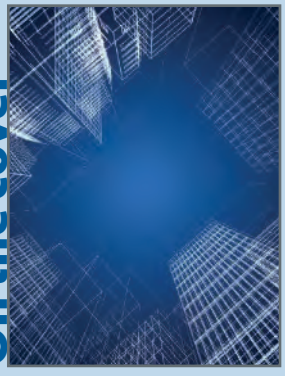

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Biosimilars or Bust

Michelle Hoffman

Are biosimilars the next big thing or just the next big bubble?

Walking the exhibit floor of an industry trade show, one becomes accustomed to seeing certain incongruities. Scattered in with bioreactors and filling lines, you can expect to see various circus performers, putting greens, and the occasional motorcycle being raffled off. But at the June 2011 Biotechnology Industry Organization (BIO) annual convention in Washington, DC, one such incongruity was not a gimmick. It was the Samsung booth, smack in the middle of the exhibit floor.

The electronics manufacturer has let its interest in the biopharmaceutical market be known for some time now. The company's $389-million investment in biosimilars was reported by *Reuters* in July 2009, who also quoted Samsung Spokesman James Chung as saying, "Biosimilars is one the businesses [sic] we aim to grow strategically. We are planning to participate (in the business) aggressively."

The initiative appears to dovetail with South Korea's plans to become a global leader in biosimilar research and development. Samsung, along with other South-Korean-based electronics firms, is contributing to a government initiative to develop the country's biosimilar industry.

It may not be as odd as it seems that an electronics company is interested in biosimilars. After all, establishing bioequivalence between innovator and follow-on biologics will require a great deal of analytics, which might make use of electronic sensors and components. The oddity is that Samsung intends to actually manufacture biosimilars.

There is disturbing variability in market projections for biosimilars.

Earlier this year, Samsung announced its partnership with Quintiles in a venture valued at $266 million, which, according to a February report by *Bloomberg*, is expected to start producing biosimilars by 2013, with most of these sales targeted at markets outside of the United States.

US companies are also getting into the market. Pfizer publicly described its interest in the sector at the BIO convention. Diem Nguyen, Pfizer's general manager for the Biosimilars Business Unit, outlined the company's intention to enter the market with some small, well-defined biologicals, including insulin, before moving into larger more complex drugs.

All of these entrants are spurred by optimistic projections of the market potential for these drugs. IMS Health released a report in July 2011 estimating that the biosimilar market will reach $2.5 billion globally by 2015. Other projections are even more enthusiastic. I thought I heard a McKinsey consultant project the biosimilar market to be $30 to $50 billion by 2020. Samsung, according to the *Bloomberg* report, is projecting its revenues from biosimilar products to possibly exceed $1.8 billion by 2020 based on its estimated demand for these medicines.

Yet, I find myself wondering: Why now? What's so compelling about this growth opportunity as opposed to, say, small-molecule generic drugs, branded monoclonal antibodies, gene therapies, or genomics-based drugs? At one time or another, each of these was deemed to be the next big thing in pharmaceuticals.

Given the anticipated difficulty in manufacturing biosimilars and the almost-certain regulatory requirement for some limited clinical data on the follow-on drugs, how much profit is there really to be made in them?

And finally, there is the disturbing variability in those market projections themselves. Is it really possible that the market will grow from $2.5 billion to $50 billion in just the five years between 2015 and 2020? Or are analysts using wildly different starting assumptions? And if they are, can we trust that anyone's model is robust?

I know we'll all be watching and reading with interest as the biosimilar story unfolds. And only time will tell whether biosimilars are the next big growth area, or just the latest high-tech bubble. **PT**

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

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Prophylaxis in a Patch

Erik Greb

New studies reveal the promise and feasibility of transdermal vaccine delivery.

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The growth in the biologics market has given the industry an extra incentive to find painless ways of administering vaccines. Recent animal studies indicate that the transdermal route could be a viable option.

Researchers from the Georgia Institute of Technology vaccinated mice against influenza using patches that contained dissolving microneedles. This administration method provided at least as much protection as traditional hypodermic injections, according to their July 2010 article in *Nature Medicine*.

A $10-million grant from the National Institutes of Health will enable the researchers, in cooperation with Emory University, to develop the patch further and conduct a Phase I clinical trial. The patch uses a dry form of the vaccine, and the team will study its stability to determine whether it can be stored without refrigeration.

Another goal of the study is to ensure that the patch is simple and reliable enough for any patient to use without assistance, says Mark Prausnitz, the project's principal investigator. If the study is successful, the patch eventually could become a more popular delivery device than autoinjectors.

Until recently, transdermal delivery had been restricted to small and lipophilic molecules. Projects such as Prausnitz's open the possibility that vaccines and other large-molecule drugs could be given effectively through the skin. Such easy and painless administration could have big benefits for public health. For needlephobes and drug-delivery scientists alike, the prospects are exciting. **PT**

Erik Greb is an associate editor of *Pharmaceutical Technology*.

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

Taking a trip—to a new site or down memory lane—may not get you where you want to go.

Rebottled

"The new stability supervisor was using a standard inventory request form to order bottles and caps for repacking bulk tablets into suitably sized stability samples," began our GMP Agent-In-Place. "When he realized he had ordered an excess of some fancy, clear over-the-counter bottles with screw caps, he decided that instead of storing them or throwing them away, he'd take them home. They ended up being used to bottle homegrown and dried herbs for his family Christmas gifts that year."

Noncompliant elevators

"Occupational safety and health administration compliance isn't my job," our GMP Agent-In-Place chuckled. "So when I saw two employees in a clinch in our freight-only elevator (employees are not allowed to use it), I didn't worry about it. I also didn't tell their spouses."

Super blank slate

"One employee held several positions within our site, each one more responsible than the last," noted our GMP Agent-In-Place. "This was back before computers and electronic-filing systems became ubiquitous. When it came time to move offices, this person fit all his files in a shoebox—and most of the items were personal, not work-related. I guess he thought everything he needed would be at the new office."

Cutting up at work

"It started as a complaint of foreign debris present in sterile solution found at a customer's location," grumbled our GMP Agent-In-Place. "We examined inspection rejects for two current batches of the same product and found similar debris, so we knew the compliant had validity. Our outside laboratory determined that all three debris samples were identical, and that they were Tyvek. Since the Tyvek also had silicone on it, the source was determined to be the stopper bags. We sterilized our stoppers in Tyvek bags, and cut them open in the sterile suite for use. Apparently, in some cases, the operator cut twice, giving a chance for Tyvek pieces to fall into the stopper hopper, and to be transferred to the solution *via* the inner surface of the stopper.

I guess he thought everything he needed would be at the new office.

"To prevent recurrence, we changed the configuration of the stopper bag to use less Tyvek, making the bag more difficult to cut and prevent the need for double cutting. The operators were retrained but, unfortunately, the bag changes required a sterilization revalidation," our Agent finished.

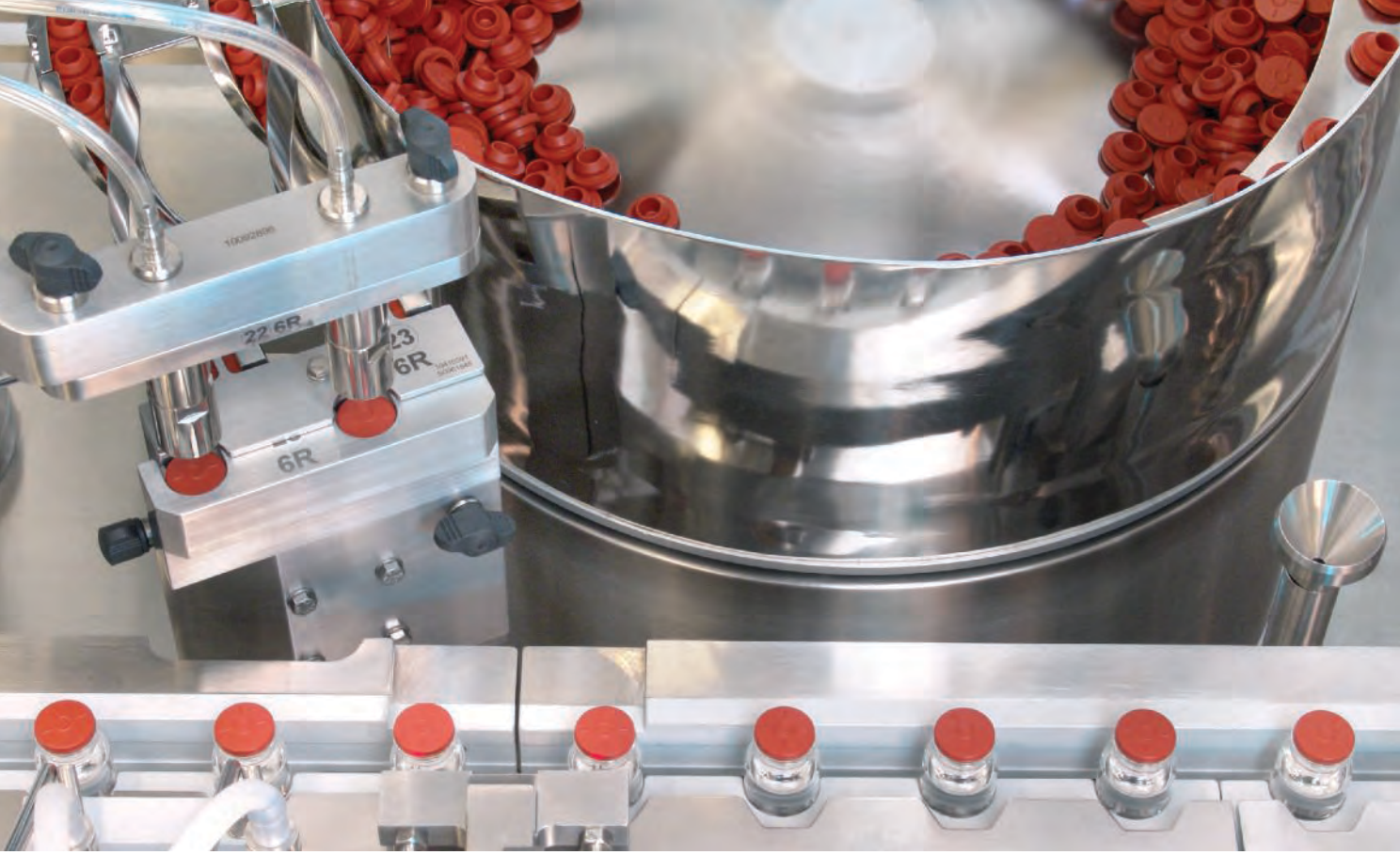
Gone missing

"For certain biological products, a sterility test has to be performed for the bulk sterile material," our GMP Agent-In-Place explains. "This requires that a sample be taken. On this fateful day, the sterility sample for one batch was missing. The batch record documented that the sample had been taken and signed for, but the sample could not be found. The sterility test could not be completed and the batch was rejected. It was suspected that the samples were waiting for seals to be transferred into the filling area, and were inadvertently discarded."

Environmental error

"I hate computers," complained our GMP Agent-In-Place. "I had to review the validation for changes to our enterprise management system and found that five different scripts were tested in the wrong system environment. We have environments labeled sandbox, development, quality, validation, production, and more. Each one is set up on a separate computer server and uses different software. There was a deviation covering these cases, and the documentation said the cases were rerun in the correct environment, but that was inadequate. For example, the response did not identify how the error was determined nor did it offer assurance that the error was limited to the five listed scripts. In the end, we had to check all the scripts. We realized that our initial training of some contract employees was lax in this regard, and was corrected before the next validation runs." **PT**

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



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In the Field

Report from: Asia

Jane Wan

Contract manufacturing organizations throughout Asia are increasing their capabilities to meet market demand and attract foreign investment and partnerships.

Asia's biomanufacturing industry has a lot to live up to in the coming years. A Business Monitor International (BMI) report projects that Asia's share of global biopharmaceutical manufacturing facilities alone will double between 2009 and 2013, growing from 10% to 20% of global market share. Asian contract manufacturing organizations (CMOs) are most likely to benefit from the growth. Multinational companies are looking to outsource in order to combat escalating costs at home. To compete, Asian CMOs are making fast strides to comply with FDA and EMA standards and requirements. *contin. on page 20*

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To date, India has the highest number of FDA-certified manufacturing facilities and more than four times the number of drug-manufacturing staff than does the United States (India has more than 12 times the number of manufacturing staff than the United Kingdom). Also, China is working hard to address its intellectual property (IP) rights issues. In 2007, the government issued 53 regulations related to drug-approval process improvement and shortened its timeframe for investigational new drugs by half.

Industry players have also expressed confidence in Asian developed countries such as South Korea and Singapore. These countries have well-established manufacturing environments and promising government initiatives. For example, Singapore's biomedical integrated strategy, launched in June 2000, has attracted big players, including Lonza and Novartis, to set up shop in its country. In June 2011, Lonza committed an additional $12.2 (CHF$10) million to further expand its Singapore plant in response to the country's positive economic growth and the government's continued support for the biopharmaceutical manufacturing sector.

To keep up with the ongoing and expected growth in biopharmaceutical manufacturing, domestic Asian CMOs are implementing a few changes to attract more global attention, including partnerships and investment.

Upgrading technology

In recent years, many pharmaceutical companies have shifted their focus from straight manufacturing to innovation, productivity, and quality control. Use of new technologies that are cost-effective and require minimal maintenance is growing more than ever before. Single-use technology, or disposables, in particular, is becoming more popular among CMOs based in Asia. The technology makes CMOs more attractive because it reduces production complexity and extends the range of services that can be offered to global customers.

Jay Chandran, associate research director of the healthcare division Asia Pacific for Frost & Sullivan, says, "[Single-use technology] will gain popularity in Asia in due course as it becomes a mandatory manufacturing capability to have if manufacturers want to remain competitive in the export markets of North America and Europe. Collaboration with large international players will further encourage the use of this technology in Asia."

In 2008, San Diego-based Pacific Biopharma Group and PacificGMP partnered to establish a single-use facility called China Quantitative Biomedicine in Taizhou, China. The facility will manufacture proteins for the US and European markets, and aims to meet the rising demands in Asia.

Unique partnerships

Four to five years ago, the way to gain access to biomanufacturing was by outsourcing to CMOs through traditional procurement processes, or by building or acquiring facilities to assert control in supply. In recent years, there has been a paradigm shift toward merger-and-acquisition (M&A) strategies.

Michael Banks, head of sales and business development for biological manufacturing at Lonza, says, "The strategies are diverse, including local or CMO–border partnerships, outsourcing strategy, and manufacturing optimization. As it has a lot to do with increased cost pressure, the shift is a result of accumulative technical experience and maturing of technologies."

Interestingly, many companies outside the pharmaceutical business are taking a plunge into the biomanufacturing market as well. In February 2011, Japan's Fujifilm announced that it will acquire Merck's Biomanufacturing Network for $490 million. South Korea's Samsung established a joint venture with Quintiles (Durham, North Carolina), whereby the latter will commit $30 million to support Samsung's entry into the biopharmaceutical market.

The move by these high-tech companies bears significance for the industry. "These are positive CMO–industrial moves for the biologics market," says Banks. "In the long run, it will strengthen the biomanufacturing value chain and fuel a full-fledged regional supply chain involving raw materials, talent, and various adjacent CMO establishments. These ancillary factors will further encourage the growth of the Asian innovator's pipeline and contribute significantly to the health of the global biopharma market in the near future."

Training and education

A key challenge facing the biomanufacturing business in Asia is gaining access to an experienced workforce. According to Banks, "Biomanufacturing is a young sector and a people business. It is therefore important to develop, troubleshoot, and optimize the processes, and ensure know-how and expertise to achieve timely delivery and cost effectiveness."

To get ahead in this area, Lonza, for instance, has trained the majority of its workforce under the Strategic Attachment and Training program with the Singapore Economic Development Board in Singapore.

Conclusion

Overall, the biologics market is predicted to be next area of growth in Asia and globally as companies aim to compensate for their potential loss of revenues from current small-molecule blockbusters. Many companies have already embarked on biologics programs, facility establishments, and related partnerships and acquisitions. Flexibility will be crucial, says Banks. "It is important to address to both market and technological demands. As a biomanufacturer, it is imperative to consider market segments and production demand instead of focusing only on blockbuster drug development and orphan drugs," he says.

Jane Wan is a freelance writer based in Singapore

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Global Healthcare on the Ground

NIH Aims to Help Treat 200 Rare Diseases

Angie Drakulich

Rare diseases are those that affect populations of 200,000 or less in the United States. Approximately 7000 such diseases, including certain congenital conditions and rare cancers, exist in the US, and they affect nearly 25 million Americans. New drug applications for these diseases can be submitted simultaneously to FDA and EMA and receive priority review under orphan-drug provisions, and multiple grant programs exist for rare-disease research. For years, many bio/pharmaceutical companies have turned a blind eye to developing products for rare diseases because such medicines have a small consumer base, and thus fall short of meeting desired revenues. Efforts to pay attention to these conditions and find cures for them, however, are gaining momentum.

Why now? According to Steve Groft, director of the National Institutes of Health (NIH) Office of Rare Diseases Research, industry and regulators have reached a point where guidance can be provided in this area. "There has not been tremendous interest in rare disease research and treatments until the past 5 to 8 years," he explains. "There was some interest in the 1980s after the Orphan Drug Act was passed in the US, but then we had the consolidation of the pharma industry, which led to an emphasis on larger blockbuster drugs. In 2000, Europe developed its orphan-drug legislation, and that stimulated more product development in this area. Today, industry realizes there are niche markets available for rare-disease treatments and that it can be a profitable market. There is increased interaction between the scientific and the patient-advocacy communities. And, most important, we are now able to look at results of years of basic research on rare diseases and better understand them," he says.

Groft is part of a unique project that began in October 2010 to develop a diagnostic tool for most known rare diseases. Known as the International Rare Disease Research Consortium, NIH and the European Commission are leading the global scientific community to find treatments for the world's most disregarded medical syndromes and conditions.

The consortium's first target is no drop in the bucket—the goal is to find new therapies for 200 rare diseases by the year 2020. "There is no list of targeted diseases yet," says Groft. "This is the master goal. We're just beginning to identify possible compounds and diseases that may be considered—some may be used for multiple diseases—and to enter them into clinical studies." The project involves research and development into new molecular entities as well as looking at already approved drugs to see whether they can be repurposed for rare diseases and made available to new populations. "Currently, only 10 to 20 products are approved per year for all diseases, and we feel there is a need to do better than that," adds Groft.

To meet its goal, the consortium would like to see harmonization of clinical trials for small patient populations and the standardization of trial-data collection. "We need global acceptance of how to do the trials, and we need patients from many different countries to have enough to complete a study more quickly. We're trying to develop a plan and process that people can use to coordinate efforts to better minimize redundant research," explains Groft. If research-data collection efforts can be standardized in a common protocol, drug-product developers will be able to use and submit that data to regulatory agencies in a much easier way—and the regulatory authorities will receive better research results to evaluate.

Common data elements can also provide a framework for patient registries to be developed and, looking ahead, says Groft, scientists may be able to use that information for natural-history studies and to develop biomarkers for clinical trials. "We should be able to do the same thing for rare diseases that is being done for cancers and for HIV/AIDS products," he says. Public communication and distribution of the information are also part of the plan.

The consortium plans to build on already existing models for some rare diseases that have received more attention than others over the years, such as certain muscular dystrophy conditions and cystic fibrosis. "These discovery and development efforts have taken a global approach, and we can use those as examples and build on those successes," says Groft. For example, the consortium would like to have the same analytical tools available on all project-relevant clinical-trial sites and the services of a data-coordination center.

NIH is also working with FDA to create a national policy for rare-disease research and related drug regulation. FDA boosted its own rare-disease efforts this past year with a newly created position in the Center for Drug Evaluation and Research, an Associate Director for Rare Diseases, and the launch of a free searchable database that lists approved compounds and products that may help researchers in their search for treatments for rare diseases. "Overall, this is an opportunity to facilitate partnerships," says Groft. "We've been talking about rare diseases for years. Individuals have been developing many of these pieces, and now is the appropriate time to put all those pieces together. The result should be a larger number of products available for the rare-disease community."

For more information, contact NIH's Dr. Groft (stephen.groft@nih.gov) or the EC's Catherine Berens (Catherine.BERENS@ec.europa.edu). To listen to a podcast interview about NIH's global health efforts with Director Francis S. Collins, visit PharmTech.com.

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Zone in on: Biomanufacturing

The Economic Contribution of the US Biopharmaceutical Indsutry

Amy Ritter

The negotiations under way to control government spending and reduce the deficit have the potential to impact pharmaceutical revenues. A proposal is on the table to increase drug rebates under Medicare Part D as a means of controlling the overall costs of the Medicare program. The Pharmaceutical Research and Manufacturers of America (PhRMA) is opposed to such measures, concerned that a decrease in revenues could damage a healthy and growing industry and that the ripple-effects from a slowdown in biopharmaceutical growth could negatively impact an already fragile economy. In a press release, PhRMA president and CEO John J. Castellani issued the following statement:

"At a time when the [US] is facing a jobs crisis, evidenced by the terrible employment numbers from last Friday, it is critical that our policymakers embrace dynamic and innovative business sectors such as the biopharmaceutical research sector and refrain from stifling job growth through shortsighted proposals such as government-mandated price controls in Medicare Part D."

PhRMA cited a newly-released report to back its assertions. The report, commissioned by PhRMA and conducted by Battelle Technology, an independent research organization, examined the direct, indirect, and induced impacts of the biopharmaceutical industry on the US economy. Direct impacts are defined as the specific impact of biopharmaceutical sector expenditures in the first round of spending. Indirect impacts are the impact of expenditures by suppliers to the biopharmaceutical sector, and induced impacts are the additional economic impact of the spending of biopharmaceutical sector employees and suppliers' employees in the overall economy that can be attributed to the direct biopharmaceutical industry expenditures.

The report found that the industry directly creates 674,000 jobs and supports an additional 3.4 million indirect and induced jobs. It directly generates $19.8 billion in state, local, and federal taxes, and including indirect and induced sources, generates around $85 billion in tax revenue. The finding that there is a large multiplier effect, that expenditures and losses by the biopharmaceutical industry are magnified by impacts on the other industries it supports, leads to the report's conclusions that a change in revenue (up or down) of $20 billion would result in a change in the economy as a whole of $58 billion.

According to Castellani, "The bottom line is we are at a critical time for our economy. We have to create jobs, not lose more. We have to support innovation, not interfere with the most innovative sectors of our economy. We must continue to improve the health of America's seniors, not increase costs and erect barriers to promising scientific breakthroughs."

CSR and sustainability forum

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

- A report on building local pharmaceutical scientific capacity in the developing world
- Innovative approaches to supply-chain management in global health
- A roundup of CSR and sustainability news.

We welcome your ideas to learn about the work of your company or organization in CSR and sustainability. Contact Patricia Van Arnum, senior editor, at pvanarnum@advanstar.com.

»PharmTech Poll

Do you think shared audits can be a tool to help manage the pharmaceutical supply chain?

71% Yes

9% No

17% Maybe

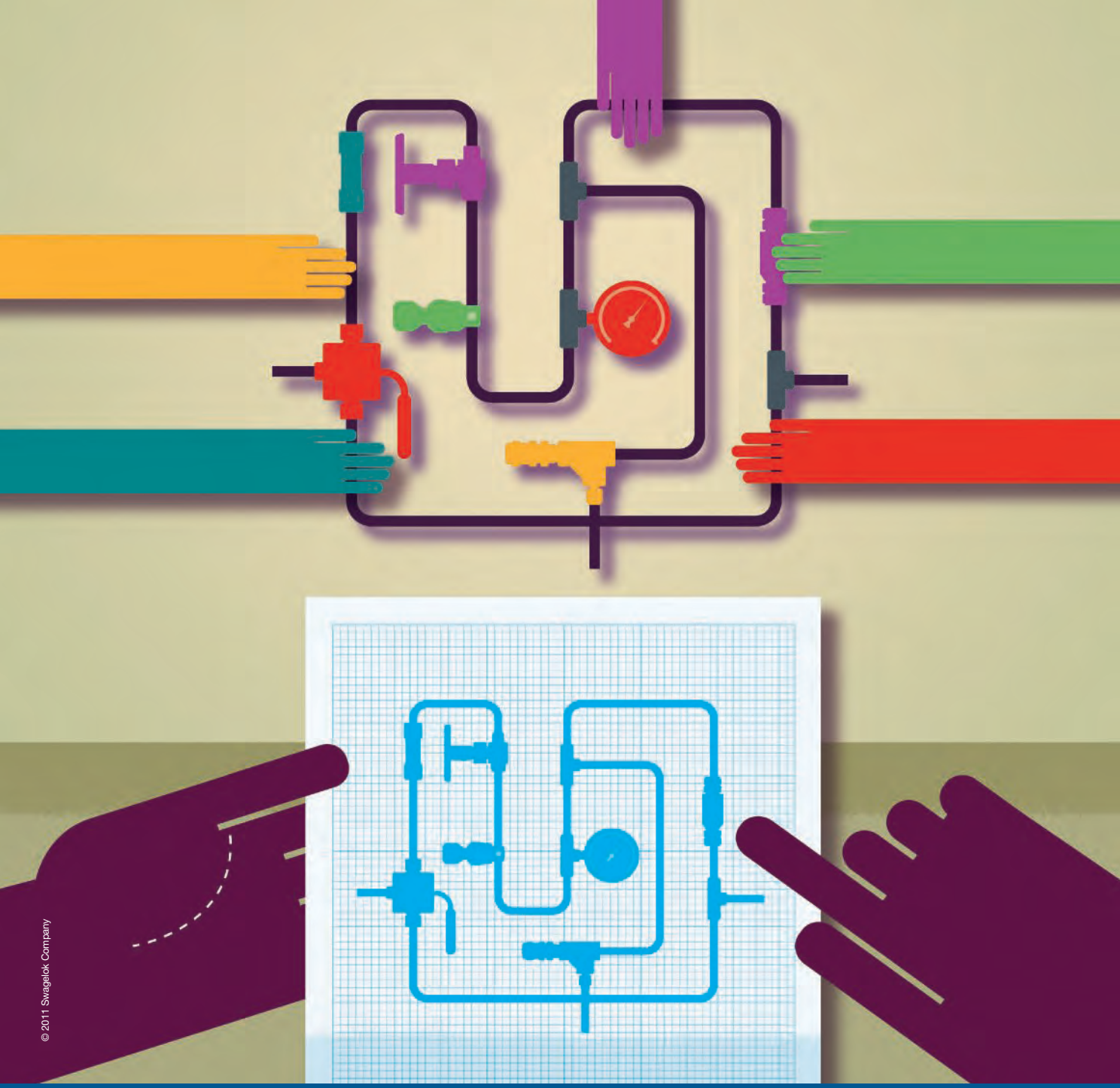
4% Don't know

Vote and view other online polls at: **PharmTech.com/polls**

FDA on Targeted Drug Therapies

FDA issued a draft guidance for industry that contains proposed policy for diagnostic tests used with targeted drug therapies (i.e., personalized medicine). Companion diagnostics are used to help healthcare professionals determine whether a patient with a particular disease or condition should receive a particular drug therapy or how much of the drug to give, according to the press release about the guidance. In addition to defining a companion diagnostic and its use, the draft guidance calls for early engagement between FDA and manufacturers so that the agency's expectations can be included in development plans, and states that FDA will aim to conduct simultaneous reviews of a drug or biologic therapy and its corresponding companion diagnostic. The document also notes instances in which the agency may approve a targeted medicine in the absence of a cleared or approved companion diagnostic (e.g., in cases where the therapy is intended to treat a serious or life-threatening disease or condition for which there is no available or satisfactory treatment and when the potential benefits outweigh the risks of not having a cleared or approved companion diagnostic, states the release). Comments on the draft guidance are due Sept. 12, 2011.

—Angie Drakulich



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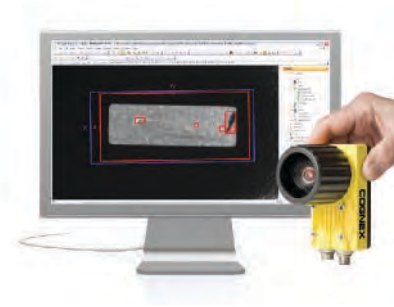
Editors' Picks of Pharmaceutical Science & Technology Innovations

Automation, already a fact of life in the pharmaceutical industry, has become even more important now that many manufacturers must reduce costs to remain competitive. Automated equipment can reduce expenses by increasing productivity and efficiency. This month's products illustrate some of the applications that this equipment can perform. A packaging machine from Uhlmann places solid dosage forms into bottles of various shapes. A vision-inspection system from Cognex can check print and detect defects. Cole-Parmer's bioreactor automatically controls cells' growth environment.



In-Sight Explorer 4.5 inspection tool
Cognex
www.cognex.com

Bioreactor controls growth variables

Cole-Parmer's IKA BR 10 bioreactor is designed to ensure the optimal cell growth of phototrophic organisms, including algae and many species of bacteria. Through a human–machine interface, operators can set timers to control the lighting, motion, pH, and temperature within the bioreactor. An in-line DC motor connected to a PTFE stirrer controls the motion within the unit. The motor can operate at low speeds for gentle agitation that provides good oxygen transfer without damaging fragile cells. Users can easily remove the motor by adjusting one thumbscrew.

The system monitors and controls pH through an automatic carbon-dioxide valve. A separate probe monitors the temperature of the vessel. Users can connect the outer jacket to a recirculation bath for optimal temperature control. A glass sparger tube provides constant oxygen transfer and mixes carbon dioxide. The 10-L bioreactor can be used as a modeling tool for scale-up applications and can be customized for specific applications.

IKA BR 10 bioreactor
Cole-Parmer
www.coleparmer.com

Inspection tool detects defects

Cognex's In-Sight Explorer 4.5 inspection tool includes an all-in-one edge- and surface-inspection tool, and an all-in-one bead-width and position tool. The software's identification-code tool reads multiple codes at one time, thus allowing In-Sight cameras to read barcodes and provide inspections simultaneously.

The product's Flexible Flaw Detection (FFD) edge- and surface-inspection tool is suitable for color and grayscale applications. The FFD tool inspects for boundary defects, such as conformity of shape, and surface defects, such as stains and scratches. FFD can also perform print inspections (e.g., inspecting screened logos for defects). FFD gives users the flexibility to select accuracy and speed requirements, and to ignore defects during system run time.

The In-Sight Explorer 4.5 product also includes two EasyBuilder user-interface tools. The Bead Finder and Bead Tracker tools find positional defects and width-based defects and gaps, and also provide bead data needed for process control.

Machine bottles solid-doses

The modular Integrated Bottle Packaging Center 120 (IBC-120) from Uhlmann Packaging Systems packages small- to medium-sized batches at a rate of 150 bottles/min and can process round, rectangular, and oval bottles of 45–200 mm in height and 25–125 mm in diameter. Its compact, 5-m monoblock design performs essential functions for packaging solid-dose products in bottles.

IBC-120 packaging unit
Uhlmann Packaging Systems
www.uhlmannpackaging.com

New Product Announcements

may be sent to New Products Editor, *Pharmaceutical Technology*, 485 Route One South, Building F, First Floor, Iselin, NJ 08830, fax 732.596.0005, ptpress@advanstar.com.

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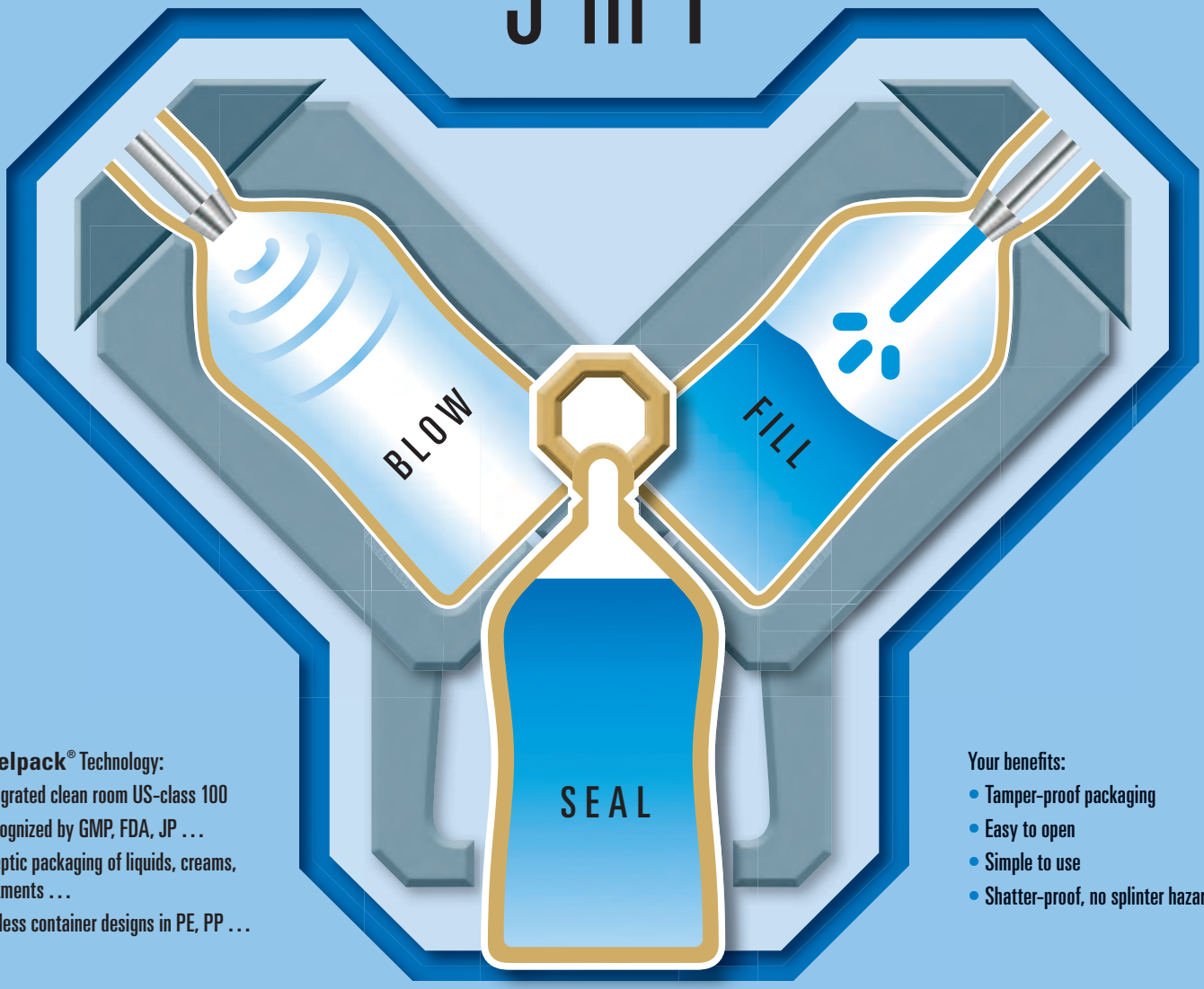

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FDA Maps Strategy to Counter Supply-Chain Threats

Jill Wechsler

Rising imports and overseas production spur realignment of enforcement activities.

Food and Drug Administration officials acknowledge that its established system for ensuring the quality of medical products marketed in the United States cannot cope with the soaring volume of pharmaceuticals and active ingredients coming into the country from all over the world. Because of the potential for consumer harm from intentional adulteration, fraud, and counterfeiting, these developments require major changes in the way FDA does business. Instead of sending inspectors abroad to scrutinize foreign facilities or trying to examine more products at US borders than before, agency officials seek to collaborate more with other regulatory authorities, to make greater use of third-party auditors, and to establish global-information networks that can better alert officials to potential safety hazards.

The call for a new approach to food and drug regulation will have a notable impact on FDA field inspections and compliance operations. The Office of Compliance (OC) in FDA's Center for Drug Evaluation and Research (CDER) has reorganized to heighten its focus on supply chain and international issues. At the same time, manufacturers are supporting new approaches and collaborative efforts to prevent drug theft, diversion, and distribution of counterfeit products around the world. These changes also reflect FDA's need to cope with increasingly tight resources at government agencies and healthcare organizations. FDA faces a potential $250-million reduction in its budget for fiscal year 2012, which begins Oct. 1, 2011, as Congress moves to cut funding for most federal programs. Such a cut would severely limit funds for FDA field inspections in all regions and limit the increased oversight of food producers and imports that has been mandated by new food-safety legislation.

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Global challenges

The lines between domestic and foreign production are increasingly blurred. The difficulties of ensuring the safety and quality of imported food and drugs in such a world are outlined in the report, "Pathway to Global Product Safety and Quality," which FDA Commissioner Margaret Hamburg unveiled in June 2011. Although the report contains few really new proposals for overseeing food and drug imports and outsourced production, the document is noteworthy for providing a comprehensive overview of the forces reshaping biopharmaceutical product development.

In the face of pressure to cut costs and increase productivity, pharmaceutical companies are shifting manufacturing to foreign locations and searching for less expensive ingredients. The cost of formulating an active pharmaceutical ingredient (API) is 15% to 40% less expensive in India, than in the US. Consequently, drug manufacturers now import 80% of APIs, primarily from China and India. Imports of pharmaceutical products have increased about 13% per year for the past seven years. This shift is boosting the US trade deficit in pharmaceutical products, which has jumped from less than $2 billion in 2000 to $18 billion in 2008.

Additional overseas outsourcing, however, fragments the drug-production process. Contract manufacturing has more than doubled during the past decade to an estimated $46 billion business in 2010. China and India now have the largest number of foreign, FDA-registered drug manufacturing establishments. These and other emerging nations also are producing more complex, high-risk biologics, and vaccines and are becoming more prominent in biopharmaceutical research and development (R&D). India and China already have more than 30% of the world's drug master files, and more clinical trials are taking place in these regions. With a growing volume of foreign manufacturers and producers to monitor, FDA concedes that it is not viable to scale up its current regulatory model, even if it had the resources to do so.

These developments inevitably open the door to more economically-motivated abuse, drug counterfeiting, fraud, and intentional adulteration. The FDA report observes that it has become "difficult to identify the 'source' of a product and to ensure that all players along the supply chain meet with safety and quality responsibilities." The US already has suffered the consequences of adulterated heparin and

In Washington this month

- Fiscal Year 2012 budget cuts could significantly reduce FDA's field inspections.
- Regulators seek collaborations that pool resources in a way that can help manage the global pharmaceutical inventory.
- FDA implements internal reorganization within CDER's Office of Compliance.

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counterfeit glucose-monitoring strips, and low-quality counterfeit medicines are widely available, particularly in developing countries. Americans feed illegal operators, moreover, by purchasing pharmaceuticals online, often from unknown sources and without oversight and safeguards.

Call for collaboration

In response, FDA proposes a more collaborative regulatory approach, somewhat along the lines of the International Civil Aviation Organization, which promotes common global standards for aviation safety. Another model is information sharing, promoted by the International Criminal Police Organization (Interpol). Access to international data on manufacturers, pharmaceutical suppliers, and regulatory operations would help FDA identify potential risks that can be monitored and addressed before they lead to public harm.

Although FDA has been engaging foreign regulatory counterparts in collaborative initiatives as well as in joint inspection and information-sharing pilot programs, these partnerships "are not sufficient" to deal with an increasingly complex global environment, the report concedes. What is needed are "global coalitions of regulators" that allow countries to maintain sovereignty in setting standards and making decisions, but rely more on the work of other regulators and encourage the pooling of resources to manage the global pharmaceutical inventory. Increased information sharing with trusted counterparts would be easier if FDA did not need to redact all trade secret information from documents, for example, a process that seriously stymies the communications process.

Such collaboration reflects FDA's recognition that its own inspectors cannot reach the growing volume of foreign sites: The average cost of a foreign-plant inspection is $52,000, more than twice the $23,000 outlay for a domestic site visit. More than 54% of foreign drug making facilities went uninspected from 2002 to 2007, and the record is even worse for foreign medical device producers. Even though FDA increased foreign-drug inspections by 27% between 2007 and 2009 and opened a series of international offices, that still falls hopelessly short of covering the field.

The good news is that collaborative initiatives are proliferating as regulators seek to conserve their own resources. Mexico and Costa Rica, for example, are accepting FDA medical-device review decisions. FDA recently put a company on import alert based on an inspection report from a European agency, and is exploring other ways to streamline operations. EMA reliance on "qualified persons" employed by drug manufacturers to verify the quality and safety of all approved drug batches is an approach worth looking at, says OC Director Deborah Autor*. She's also interested in models for third-party audits for drugs, an option already authorized by FDA for medical devices and food imports. A shift to more reliance on outside auditors, however, requires a more sophisticated review and monitoring infrastructure that can verify the integrity of information received from other regulators and private parties.

Related initiatives aim to expand the expertise and capabilities of regulatory agen-

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EXHIBITION: September 19-20 | **POST CONFERENCE WORKSHOP:** September 21-22 | **COURSES:** September 22-23

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Other Program Highlights Include:

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  - This session will cover recent biotechnology business and regulatory trends and business. FDA representatives will discuss pre-approval inspection trends and case studies. The latest trends in the biotech business will also be covered by a leading pharmaceutical executive.
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    - Biotech Pre-Approval Inspection Findings: **Patricia Hughes**, Lead, Consumer Safety Officer, *DMPQ, CDER, FDA*
    - Biotech Inspection Trends: **Azita Gerhardt**, President, Global Pharmaceutical Operations, *Abbott Laboratories*
    - Biotechnology Inspections (pre-Approval and Biennial): An FDA Product Quality Reviewer's Perspective: **Laurie Graham**, Biologist, *OBP, CDER*
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PDA will also be hosting a post conference workshop: *PDA 2011 Combination Products Workshop* on September 21-22, 2011.

For details and to register, visit www.pda.org/pdafda2011

ICH spreads global standards

Pharmaceutical manufacturers and regulators in the US, Europe, and Japan are bringing regulatory authorities and health organizations from other regions under the International Conference on Harmonization (ICH) umbrella. When ICH was established in 1990, most pharmaceutical research and development, and manufacturing took place in the EU, the US, and Japan, observed Mike Ward, director for international programs at the Health Canada Therapeutic Products Directorate. The pharmaceutical world has changed greatly in the past 20 years, making it important to reduce country and regional differences in technical requirements for medicines, he commented at an FDA public meeting in June 2011 that discussed ICH expert working-group activities.

ICH began inviting more "interested parties" to participate in expert working groups several years ago and established a Regulators Forum in 2008 to communicate ICH policies to authorities in emerging countries such as China, India, and Brazil. The ICH Global Cooperation Group now broadly transmits ICH deliberations and decisions. Active regulatory authorities and regional harmonization initiatives, such as the Association of the Southeast Asian Nations and the Pan American Network for Drug Regulatory Harmonization, may become regular expert working group participants. "The continued success and relevance of ICH," says Justina Molzon, associate director for international programs within CDER at FDA, "will depend on a much broader use of ICH guidelines and standards."

cies around the world. The World Bank is providing resources for building regulatory capacity in developing economies so that less-experienced agencies can better enforce GMPs and other drug quality policies. The US Pharmacopeia similarly is providing technical assistance to help emerging-nation manufacturers comply with GMPs, along with support for regulatory authorities to establish quality drug-surveillance programs. The US Agency for International Development (USAID) funds this $35 million, 5-year program, which now is active in about 30 countries in Africa, Asia, and Latin America. A major impetus for regulatory capacity building comes from donor and health funding organizations, such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which increasingly require the drugs they purchase to meet GMPs and World Health Organization prequalification standards.

Pharmaceutical companies also are working together to prevent product theft and adulteration and to provide more efficient ways to oversee suppliers and contractors. The Rx-60 consortium aims to ensure product quality through cooperative auditing of suppliers and contractors. More than 50 pharmaceutical, biotech, and supplier companies are participating in the Rx–360 shared audit program, which uses third-party auditors to examine operations and standards at producers of active ingredients, excipients, and other raw materials. The program encourages companies to provide their own audits of suppliers.

Separately, several organizations market third-party audit and certification programs for excipients. A new track-and-trace consortium of manufacturers, distributors, pharmacists, and shippers is

working with FDA to develop standards for an interoperable prescription-drug tracking system. The impetus comes from California ePedigree requirements, which are scheduled to begin in 2015.

Expanding compliance

With drug manufacturing and clinical-trial activities expanding overseas and at home, CDER's Office of Compliance is being reshaped into a "super" office that can better manage its growing responsibilities. OC now has a staff of 300, compared with 118 in 2005, explained OC Deputy Director Ilissa Bernstein at the Parenteral Drug Association pharmaceutical supply-chain conference in June. Now a string of top aides manages cross-cutting initiatives, including policy and communications, strategic planning and organization development, data analysis, and risk assessment, directly under OC Director Autor. These staff functions incorporate many of the data-management responsibilities of the former Division of Compliance Risk Management and Surveillance.

The main new OC component is the Office of Drug Security, Integrity, and Recalls (ODSIR), which will oversee import operations, recalls, and a range of supply-chain issues. An Import Operations branch will coordinate import and export compliance activities, including supplies for clinical and preclinical studies. The Division of Supply Chain Integrity (DSCI) will handle anticounterfeiting strategies, track-and-trace initiatives, product authentication, good importer practices, good distribution practices, cargo-theft prevention, intentional adulteration, and efforts to leverage domestic and international partnerships in these areas, explained Leigh Verbois, who will serve as the DSCI deputy director.

Among other responsibilities, ODSIR Acting Associate Director Connie Jung will continue to lead agency efforts to develop track-and-trace programs, building on guidance issued in March 2010 that outlines how manufacturers should provide a standard numerical identifier (SNI) on every product as the basis for tracking products through the supply chain. FDA is digesting comments from a February 2011 public workshop on how to develop interoperable standards that will facilitate adoption of pedigrees and tracking systems, hopefully in time to help manufacturers meet California requirements.

With this reorganization, OC's status is similar to that of CDER's Office of New Drugs, Office of Pharmaceutical Science, and Office of Surveillance and Epidemiology. Most OC divisions will function as before, though with slightly revised names. The Office of Manufacturing and Product Quality (OMPQ) will no longer oversee recalls and shortages, but continues to manage inspections for new and generic drugs and biologics, both domestic and international, to ensure compliance with GMPs. The Office of Unapproved Drugs and Labeling Compliance (OUDLC) oversees drug fraud and labeling and approval requirements for prescription and over-the-counter drugs. The Office of Scientific Investigations (OSI), which monitors clinical trial operations, bioequivalence testing, and patient protections, gains a new division of safety compliance with responsibility for postmarketing activities, including adverse event reporting and risk evaluation and mitigation strategies (REMS) .

The global market "contains a vast amount of counterfeit and substandard drugs," Bernstein commented at the PDA conference, noting the need for more transparency and accountability in the supply chain, both upstream and downstream.

OMPQ Associate Director Richard Friedman emphasized that company management is ultimately responsible for ensuring product quality, including use of safe and reliable raw materials and effective monitoring of outsourced activities. A significant reason for the OC reorganization, Autor explains, "is to recognize the challenges of globalization" and to be able to focus more on international collaboration, data mining, and risk analytics. "It fits together nicely and it's the right direction for us to move in." **PT**

*As we went to press, FDA announced a major reorganization of the Commissioner's office, with Autor becoming FDA Deputy Commissioner for Global Regulatory Operations and Policy. Bernstein will serve as the Office of Compliance Acting Director.

IMAGE: STOCKBYTE/GETTY IMAGES

PharmTech.com/bio

Embarking on the New World of Personalized Medicine

Albert S. Lee, Ash Malik, and Mark A. Mynhier

A path to personalized medicines creates a new paradigm for development and manufacturing.

Pharmaceutical companies are migrating away from a "one-size-fits-all" drug-development model to address crucial game-changing realities that are affecting every part of the value chain. These realities include expiring patents, competition from generic drugs, and more demanding regulations that expect new drug applications to focus on targeted therapeutics that rely on biomarkers to identify likely responders. As a result, pharmaceutical companies are changing many aspects of their business model, including how drugs are discovered, developed, manufactured, and sold (see Table I).

The result is a sweeping shift toward personalized medicines that rely on disease-profiling technologies and retooled pharmaceutical capabilities. Research and development (R&D) and product development will need to adapt more quickly to new disease-profiling techniques (e.g., genomics, proteomics, and metabolomics) and technologies (e.g., microarrays, genotyping platforms, disease models, and dynamic-system pharmacokinetic and pharmacodynamic analysis) by integrating an ecosystem of R&D partners. These new R&D practices will need to validate and characterize hypotheses around novel disease pathways and mechanisms of action rather than rely as heavily on hypothesis-free, high-throughput target analysis. By using the latest profiling technologies to identify likely responders, researchers will be able to conduct smaller, shorter, more focused, and less expensive clinical trials.

Development teams will need to integrate a group of experts, including molecular biologists, geneticists, informaticists, process scientists, instrument software/hardware engineers, sales and marketers, medical-affairs specialists, and regulatory experts to synchronize drug and companion diagnostic development and launch. Effective orchestration of these experts, practices, and technologies will require advanced product-development capabilities.

Manufacturing organizations will need to coordinate the production of drug products and companion diagnostic kits. Given smaller patient populations for each targeted molecule, drug manufacturers will adapt their high-volume operations to smaller volume operations that entail more frequent equipment changeovers, cleaning, and product-line clearances. Drug manufacturers will need to partner with and manage outsourced companion diagnostic kit manufacturers, which involves ensuring high-quality internal drug-manufacturing operations and outsourced diagnostic kit manufacturing. With more operating complexity, greater controls will be required of manufacturing, operations, including production controls, material handling, environmental monitoring, drug and kit storage and handling, and drug–device batch-record review.

The path to personalized medicine will require a capability to manage a complex, integrated set of capabilities across a broad ecosystem of partners; however, the clinical outcomes and lower overall development costs will justify the means. **PT**

Table I: Operating changes required to support personalized medicine

Area of change	Type of change
Drug discovery	Apply "omics" analyses to elucidate the mechanism of action of a disease pathway to identify drug targets
Translational medicine	Identify biomarkers for the disease pathway that predict likely responders to the proposed drug treatment and conduct focused, adaptive trials that demonstrate heightened efficacy and safety
Companion diagnostics	Develop commercial assays that detect biomarkers in a broad range of patient samples with adequate specificity and sensitivity
Regulatory submissions	Submit smaller sets of research and clinical data that demonstrate adequacy of "omics" analyses, favorable clinical efficacy and safety outcomes, and *in vitro* diagnostics performance in meeting higher regulatory approval standards
Drug/device manufacturing	Learn to scale up and manufacture frequent batches of targeted drugs while synchronizing the launch of the companion diagnostic kits
Physician uptake	Educate and train physicians on new diagnostic methods and instruments
Marketing and sales	Market and distribute both the drug and the diagnostic kit despite notably different methods of promotion, positioning, and reimbursement
Reimbursement	Convince payers to reimburse at premium levels based on enhanced probability of efficacy and safety outcomes

"Omics" refers to genomics, proteomics, and metabolomics.

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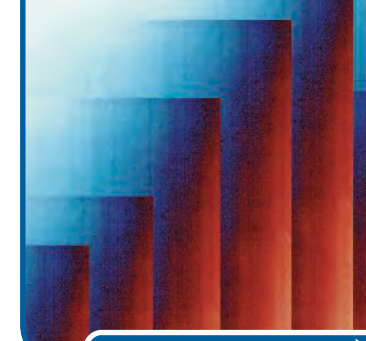

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Reducing the Risk in Risk Management

Lynn D. Torbeck

A firm grasp of probability and ongoing re-evaluation are key in mitigating risk.

Has risk management gone mainstream? One might think so given the June 13, 2011 article in the *Chicago Tribune* on using the game of poker to train stockbrokers in the nature of risk (1).

In the pharmaceutical industry, the reception of International Conference on Harmonization Guidelines Q8, Q9, and Q10 has led to widespread discussion, if not implementation, of the Quality Trio guidelines, with ICH Q9 specifically addressing risk management.

While it is perhaps too early to say that risk management has gone mainstream, it has certainly had its fair share of news coverage of late. Due to a rare 9.0 magnitude earthquake and an unprecedented 45-ft tsunami that washed over the nuclear power plant in Fukushima, three out of six reactor cores melted down—the worst possible outcome. It will take decades and billions of yen to clean up.

The world was stunned by that event. If a highly-regulated industry run by a detail-oriented and meticulous culture such as Japan made this mistake, what chance do the rest of us have at risk management? Which raises the questions, what are the risks in risk management and can we reduce them? First it is important to define terms.

In ICH Q9, risk to a patient equals probability times severity. What is probability? We can do little better than this observation from Bernoulli in 1713:

> *"For it should be presumed that a particular thing will occur or not occur in the future as many times as it has been observed, in similar circumstances, to have occurred or not occurred in the past."*
> —D. Bernouilli

This definition has been refined since then. Here are the three common definitions given:

- An undefined subjective measure of belief from personal estimate, gut feeling or intuition
- The observed frequency of outcomes, as a fraction, percentage or a proportion
- A theoretical characteristic of the situation as determined by the limiting frequency of an infinite random series.

I note with concern and dismay that ICH Q9 does not include probability in the list of definitions. Perhaps the authors assume that everyone has the same universal understanding of this complex topic, so a definition is not needed.

Severity is the second component of risk and is defined in ICH Q9 as "a measure of the possible consequences of a hazard" (i.e., a meltdown). Now, let's turn to key steps for mitigating the risk in risk management.

Include top management. They can delegate work but not the responsibility of a mission critical process. Note that risk management is a not an event but an ongoing reevaluation. Management must fight the danger of complacency, distraction, and stagnation. Risk analysis cannot simply become window dressing for the regulators. Risk reduction is costly, and management reflects the importance of the task with support, finances, and resources.

At least one person in the risk team must understand probability well enough to teach it to the other members. Few people have studied probability and even fewer have practical experience of using probability. Real life probability estimation is much more difficult than textbook exercises. Yet, probability theory is the core of determining risk.

Risk assessment cannot be seen as a check-the-box activity; it is a serious issue and requires serious effort and commitment. The success of the assessment is a direct result of the skill, education, and experience of the company's team members. Technical experts are absolutely necessary even if external experts must be called in. All stakeholders must work to agreement.

Industry in general is less interested in the risk of an everyday occurrence, such as the risk of failing the moisture test for the next production run. What is more important is estimating risks

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PharmTech.com/pack

Performing Double Duty

Hallie Forcinio

Many child-safe package designs help improve compliance and provide tamper evidence.

Child-resistant (CR) packaging is typically associated with closures that require two simultaneous actions (e.g., squeezing and turning or pressing and turning) or a sequence of actions. In the United States, the Consumer Product Safety Commission requires CR packaging to be senior friendly (SF) as well. Designing a package that is both CR and SF poses significant challenges, but options are increasing.

For example, pharmaceutical manufacturers that prefer blister packaging traditionally have relied on multilayer lidstock laminations with a peelable paper layer to prevent access by children. However, some new structures are eliminating the paper layer to provide easier access for adults while still protecting children.

One structure incorporates layers of printed foil, adhesive, polyester, and heat-seal coating, and seals at lower temperatures than a conventional paper–polyester laminate does, thus enhancing productivity while reducing the amount of heat exposure that the product experiences. Eliminating the paper layer reduces particulate contamination (easy-PIESY Lidding, Constantia Hueck Foils).

A polyester-based lidstock not only eliminates the paper layer, but is available in three levels of CR protection. The all-film coextrusion or coextruded film–foil structure can be configured for peel, peel–push or tool-aided access to the medication inside and can be designed to meet F = 1 requirements, the highest level of child resistance that the Consumer Product Safety Commission recognizes (Safety-Pak Plus PL, PP, or LT lidstock, Winpak Heat Seal Packaging).

Wallet designs can serve as compliance packages, starter kits, or titration regimens.

For form–fill–seal packaging such as stick packs, pouches, or barrier overwraps, four standard film constructions provide different degrees of CR protection while maintaining senior friendliness, processability, and performance. The materials can be printed in as many as 10 colors to maximize shelf appeal. Solventless lamination options address sustainability initiatives because they reduce energy consumption by 86% compared with solvent-based laminating processes. Structures compatible with high-speed equipment also are available (Flexi-Free CR barrier overwrap film, Ampac Flexibles, a division of Ampac Packaging).

Another way to impart CR protection is to put a non-CR blister into a CR wallet. Many wallet designs also serve as compliance packages, starter kits, or titration regimens.

One patented wallet pack seals a non-CR blister into a paperboard sleeve to create a CR package (howell•CR•III package, Howell Packaging). A configuration using paperboard with recycled content also has earned an F = 1 rating. At least two machines can join the blister card and paperboard. One is capable of running 50–75 packs/min (wallet pack machine, Howell Packaging), and another produces more than 200/min (Blister Card/Wallet Machine, MGS Machine).

Another wallet concept relies on an open-ended, flat paperboard carton with matching oval windows in the top and bottom panels. It also incorporates a die-cut tab in the blister to lock the card in place. Pushing the die-cut tab up unlocks the blister and allows the card to slide out. An interior stop prevents the card from being completely removed from the seal- or tuck-end carton. After the user removes the dose by pushing it through the lidstock, he or she slides the card back into the car-

We'll be seeing more ...

- Child-resistant (CR) wallet packs
- CR designs with enhanced senior-friendly qualities
- Solvent-free lamination
- Packaging with recycled content
- Tube packaging

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ton and presses the tab down to lock it in place. Poly-coated paperboard protects the carton from tearing, and the configuration is often compatible with existing blister tooling. Adult testers rated the design as easy to manipulate. Toddler testers had such difficulty with access that the package earned an F = 1 rating (F1 Easy Lock wallet, Intini Marketing).

For fragile capsules or tablets, child-resistant protection is still possible.

A similar pull-out–push-in design with an F = 1 rating earned praise from the Arthritis Foundation for its ease of use. The integrated carton, blister card, and leaflet or insert features an easy push-through lidstock plus a calendar or set of dosing instructions to help the patient remember when to take a pill. To earn the commendation, the package underwent a series of rigorous tests at the Georgia Institute of Technology's Research Institute, an independent laboratory that analyzes products for people with functional limitations resulting from arthritis. The study participants, who have moderate to severe arthritis, found the design easy to use, and six out of eight participants would recommend the design to friends with arthritis (Dosepak Express, MeadWestvaco).

If a capsule or tablet is too fragile to be pushed through lidding material, CR protection is still possible through a folded, heat-sealable paperboard card with a perforated tab and a dual-chamber blister (i.e., one empty and one full chamber). To access the dose, the user tears away the paperboard tab, presses down on the empty blister chamber to break the lidstock, and tears the lidstock to free the dose in the second chamber. Suitable for clinical trials, the design also is licensed for use by the Veterans Administration (Peel Peel wallet, Intini).

For sturdier doses, a similar concept starts with pressing out a perforated tab with a key, tearing the tab away to expose the foil lidstock, and pushing the pill through (3CPak, Colonial Carton) A low-volume version for clinical trials also is available (Key-Pak, Keystone Folding Box).

A similar paperboard wallet design with perforated tabs calls for bending the edge of the wallet to gain access to the tab. When the tab is removed, a layer of paperboard with an I-shaped die cut remains. The die cut reduces the force needed to push the pill through the lidstock and paperboard layer. The intuitive design eliminates the need for printed instructions, thus leaving more space for product information and graphics.

For regimens with high pill counts, a folded double card can be housed in an open-ended, tuck-style carton. Blisters can be traditional film–foil or cold-formed foil. Ranking as the first CR and SF blister pack approved by the Canadian Standards Association, the design also meets US and European requirements for CR packaging (Bend and Peel Easy Tab wallet, Intini).

Another folded-wallet design can be assembled semiautomatically or automatically. The booklike configuration provides ample space for product information and vivid graphics (CRx Pack, Pharma Packaging Solutions, a division of Carton Service).

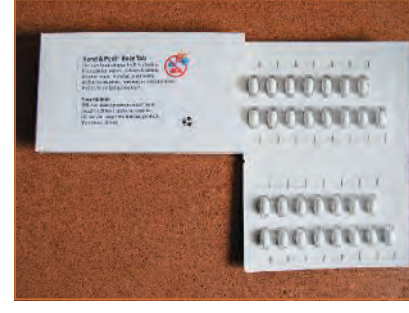
Other designs bring CR protection to injection-molded containers. Designed to be reusable, a recyclable hinged container can be sized and shaped to hold vials, blisters, aerosols, autoinjectors, patches, mists, pumps, and syringes. Releasing the lid requires two hands, one putting pressure in one area on the base of the container, and the other pressing down on latches on opposite ends of the integral lid. A version of the F = 1-rated container that holds multiple blisters could be used by pharmacies for prescriptions (Medi-Lock CR Container, Intini).

A related two-piece container dispenses doses singly while providing F = 1 protection. It can be sized to han

A tiny press-and-turn cap imparts child-resistant and tamper-evident properties to a single-dose tube.

The F = 1-rated howell•CR•III wallet can be made with virgin or recycled-content paperboard.

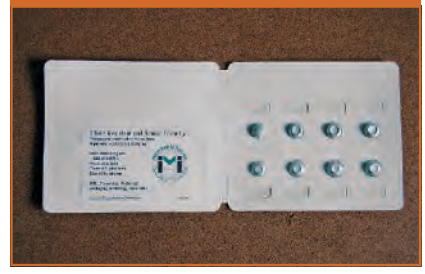
Intini's Bend and Peel Easy Tab wallet with a folded double card provides child resistance protection for high pill counts.



IMAGES (TOP TO BOTTOM): COURTESY OF NEOPAC, HOWELL PACKAGING, AND INTINI MARKETING

Intini's F = 1 Easy Lock wallet unlocks the blister card by pushing up a die-cut tab. An interior stop prevents removal of the card from the sleeve.

Most child-resistant wallet designs from Intini accept cold-formed foil blisters as well as standard blisters.



A child-resistant wallet design from Intini holds a blister card with a dual-chamber configuration to provide access to doses that are too fragile to be pushed through lidding material.

IMAGES ARE COURTESY OF INTINI MARKETING

dle virtually any tablet and is compatible with high-speed, automated filling lines (Medi-Lock Top Lock Slider Pack, Intini).

Tube packaging also has CR options. One tiny cap for single-dose tubes also offers tamper-evident protection. Like many CR concepts, the closure requires a dual movement. The outer cap rotates freely unless it is pushed in to interlock with the inner cap. Pressing and turning releases an inner pin and opens the tube at a defined breaking point, while the cap remains on the tube body during dispensing. An ergonomic nozzle enables precise application of the liquid or cream without allowing the contents to be contaminated. The design is certified as CR and suitable for adults according to testing carried out in accordance with 16 *CFR* 1700.20 and EN 14375. Applications include topical treatments, dietary supplements, concentrates or laboratory substances, product samples, and travel-size products (Twist'n'Use CR Polyfoil tube, Neopac).

For larger tubes, CR closures are available in a diameter of 18 mm (CR Tube-Lok closure, Berry Plastics). For on-the-go applications, a small integrated push-and-turn closure–vial combination holds a short stack of pills. It's offered in 16-mm or 20-mm diameters (Pursepak package, Berry Plastics). **PT**

Statistical Solutions

contin. from page 36

such as a recall or another heparin type of tragedy. The difficulty in doing so is compounded by the lack of information and actionable data. In the absence of historical data, we are left with a gut-feeling, which can often underestimate the risk. The best experts must be consulted.

> *"For every complex and difficult problem, there is a solution that is simple, intuitive, easy to understand—and completely wrong."*
> —Anonymous

Estimating probability and severity on scales of low, medium, and high (or on a scale of 0–4) are so simplistic as to be almost worthless; like using third grade English to study a college subject. Formal training in probability is needed to advance beyond this simplistic approach.

Finally, focus on the patient, build for the future, collect relevant data, and store it for easy access and analysis. Expand the knowledge base of the team and the company. Learn from others and learn advanced probability theory. Continue to refine and improve. Only through our best efforts can industry say with confidence that it understands the risks facing patients.

"Luck is probability taken personally"

Penn F. Jillette

Reference

1. N. Popper, *Chicago Tribune*, June 13, 2011. **PT**

Big Pharma's Manufacturing Blueprint for the Future

Pharmaceutical Technology's annual manufacturing investment update

Patricia Van Arnum

The pharmaceutical majors manufacturing activities in 2010 and 2011 to date have been marked by several common themes: ongoing restructuring and select investment in biologic-based manufacturing, particularly vaccines, and emerging markets. China and India continue to be targets of investment, particularly through alliances or joint ventures, and investments are being made in Russia and Brazil as well.

Company activity

Pfizer. Pfizer is continuing a restructuring of its manufacturing network, which was announced in May 2010, as part of its integration plan following its $68-billion acquisition of Wyeth in 2009. As of Dec. 31, 2010, Pfizer operated plants in 76 locations on a global basis with major manufacturing facilities in Belgium, China, Germany, Ireland, Italy, Japan, the Philippines, Puerto Rico, Singapore, and the continental United States. The company's plant network strategy calls for the exit of nine sites during the next several years, according to the company's 2010 annual filing with the US Securities and Exchange Commission (SEC).

Pfizer's strategy, as detailed in May 2010, includes plans to discontinue operations at three solid-dosage sites in Caguas, Puerto Rico; Loughbeg, Ireland; and Rouses Point, New York. Pfizer also announced plans to phase out pharmaceutical solid-dosage manufacturing in Guayama, Puerto Rico, but that site will expand its consumer-healthcare operations. Reductions are planned at two other solid-dosage facilities in Illertissen, Germany, and Newbridge, Ireland.

Two aseptic facilities that make sterile injectable medicines were targeted for exit: Dublin, Ireland, and Carolina, Puerto Rico. Pfizer also announced changes to its biopharmaceutical-manufacturing network. The company said it planned to exit operations in Shanbally, Ireland, and Pearl River, New York. The Pearl River site, however, will remain Pfizer's center of excellence for vaccine research and development (R&D). Biotechnology plants in Sanford, North Carolina, Andover, Massachusetts, and Havant, United Kingdom, are expected to see reductions.

Pfizer reported plans to cease production of consumer-healthcare products at its plant in Richmond, Virginia, but consumer healthcare R&D operations will continue in Richmond. The timing of specific exits will depend upon the complexity of operations, the amount of time needed for product transfers, and other business requirements, said Pfizer in a May 2010 press release.

In outlining the changes to its manufacturing network, Pfizer also summarized how its transformed manufacturing network will look. Pfizer's solid-dosage network will include plants in Freiburg, Germany; Amboise, France; Vega Baja and Barceloneta, Puerto Rico; Ascoli,

IMAGE: DINN / GETTY IMAGES

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Table I: Top 50 pharmaceutical companies (Rankings 1–25).

Rank	Company	2010 global pharmaceutical sales*	Sales change from 2009	R&D spending
1	Pfizer	$58.5 B	28.9%	$9.413 B
2	Novartis	$42.0 B	9.2%	$7.100 B
3	Sanofi	$40.3 B	–4.1%	$5.147 B
4	Merck & Co.	$39.8 B	58.0%	$11.00 B
5	Roche	$39.1 B	4.1%	$8.612 B
6	GlaxoSmithKline	$36.2 B	–4.2%	$6.126 B
7	AstraZeneca	$33.3 B	1.4%	$4.200 B
8	Johnson & Johnson	$22.4 B	–0.4%	$4.432 B
9	Eli Lilly	$21.1 B	5.4%	$4.880 B
10	Abbott	$19.9 B	27.7%	$3.724 B
11	Bristol-Myers Squibb	$19.5 B	3.6%	$3.566 B
12	Teva	$16.1 B	16.0%	$933 M
13	Amgen	$14.7 B	1.8%	$2.894 B
14	Bayer	$14.5 B	–3.6%	$2.320 B
15	Takeda	$14.2 B	–0.1%	$3.198 B
16	Boehringer Ingelheim	$12.9 B	–10.8%	$3.056 B
17	Novo Nordisk	$10.8 B	9.9%	$1.709 B
18	Astellas	$10.5 B	6.0%	$2.109 B
19	Daiichi Sanyko	$9.8 B	20.0%	$2.124 B
20	Eiasi	$8.4 B	8.0%	$1.932 B
21	Merck KGaA	$7.8 B	–0.4%	$1.547 B
22	Gilead Sciences	$7.4 B	14.2%	$1.073 B
23	Baxter International	$5.6 B	1.3%	$915 M
24	Mylan	$5.2 B	7.5%	$282 M
25	Servier	$4.9 B	6.6%	$1.226 B

*Sales figures are global human prescription drug sales, inclusive of generic drugs and vaccines as far as company documentation provides. In most cases, numbers are taken from annual or SEC filings for the fiscal year ended in 2010, generally Dec. 31, 2010, for US and European companies and Mar. 31, 2010, for Japanese companies. In certain instances, estimates are used. For companies reporting in curencies other than US dollars, numbers are based on the midpoint average interbank rate for the last day of the fiscal year.
Note: B is billion. M is million. R&D is research and development. N/A is not available. *Source*: The Pharm Exec 50, *Pharmaceutical Executive,* May 2011.

Italy; Newbridge, Ireland; and Illertissen, Germany. Its aseptic-manufacturing network will consist of plants in Puurs, Belgium; Perth, Australia; Catania, Italy; and Kalamazoo, Michigan. Its biotechnology-manufacturing network will consist of sites in Grange Castle, Ireland; Strangnas, Sweden; Algete, Spain; Havant, United Kingdom; Andover, Massachusetts; and Sanford, North Carolina. The consumer healthcare network will include plants in Guayama, Puerto Rico; Montreal, Canada; Albany, Georgia; Aprilia, Italy; Hsinchu, Taiwan; and Suzhou, Jiangsu, China.

Pfizer added to its manufacturing network in February 2011, when it acquired the specialty pharmaceutical company King Pharmaceuticals. As of December 2010, King Pharmaceuticals had manufacturing facilities in Bristol, Tennessee; Rochester, Michigan; Middleton, Wisconsin; and St. Petersburg, Florida, as well as an auto-injector manufacturing facility in St. Louis, according to King Pharmaceuticals' 2010 SEC annual filing.

Pfizer is further expanding its manufacturing position in emerging markets, principally through alliances. In China, Pfizer signed a memorandum of understanding (MOU) with Zhejiang Hisun Pharmaceutical in July 2011 for a possible joint venture, which will include manufacturing cooperation, local and global sales and marketing infrastructure, and R&D of off-patent medicines. In April 2011, Pfizer signed an MOU with Shanghai Pharmaceutical for a potential partnership for the registration and commercialization of innovative Pfizer products in China. The companies also are examining cooperation in distribution, commercialization, R&D, manufacturing, and equity investment. In South America, Pfizer acquired a 40% stake in Laboratório Teuto Brasileiro a generic-drug company in Brazil in November 2010.

Sanofi. In 2010, Sanofi invested nearly EUR 1.2 billion ($1.72 billion) to increase capacity and improve productivity at various production and R&D sites, according to the company's 2010 SEC annual filing. In Europe, the company invested in two new production lines at its facility in Frankfurt for Lantus (insulin glargine). The company also invested in its Brindisi, Italy, site to expand production of spiramycin, the

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Table II: Top 50 pharmaceutical companies (Rankings 26–50).

Rank	Company	2010 global pharmaceutical sales*	Sales change from 2009	R&D spending
26	Chugai	$4.6 B	1.3%	$671 M
27	Mitsubishi Tanabe	$4.4 B	2.4%	$897 M
28	Menarini	$4.0 B	0.2%	N/A
29	Genzyme	$4.0 B	2.3%	$847 M
30	Allergan	$4.0 B	7.9%	$805 M
31	Forest Laboratories	$3.9 B	7.4%	$1.054 B
32	CSL	$3.8 B	–3.6%	$272 M
33	UCB	$3.7 B	–4.0%	$1.044 B
34	Otsuka	$3.6 B	–46.1%	N/A
35	Celgene	$3.5 B	36.7%	$1.128 B
36	Biogen Idec	$3.5 B	10.1%	$1.249 B
37	Shire	$3.1 B	16.1%	$662 M
38	Alcon	$3.1 B	14.5%	$747 M
39	Warner Chilcott	$2.9 B	111.0%	$147 M
40	Cephalon	$2.8 B	28.3%	$440 M
41	Watson	$2.6 B	27.0%	$296 M
42	Lundbeck	$2.6 B	–0.6%	$542 M
43	Kyowa Hakko Kirin	$2.6 B	14.7%	$429 M
44	Dainippon Sumitomo	$2.6 B	20.1%	$554 M
45	Shionogi	$2.4 B	35.2%	$135 M
46	Actavis	$2.4 B	32.5%	N/A
47	Hospira	$2.3 B	13.3%	$301 M
48	Nycomed	$2.2 B	–20.2%	$281 M
49	Apotex	$2.1 B	–19.2%	N/A
50	Stada	$2.1 B	–5.0%	$73 M

*Sales figures are global human prescription drug sales, inclusive of generic drugs and vaccines as far as company documentation provides. In most cases, numbers are taken from annual or SEC filings for the fiscal year ended in 2010, generally Dec. 31, 2010, for US and European companies and Mar. 31, 2010 ,for Japanese companies. In certain instances, estimates are used. For companies reporting in curencies other than US dollars, numbers are based on the midpoint average interbank rate for the last day of the fiscal year.
Note: B is billion. M is million. R&D is research and development. N/A is not available. *Source:* The Pharm Exec 50, *Pharmaceutical Executive,* May 2011.

active ingredient of the antibiotic Rovamycin. In the US, the company is investing in epiCard, a gas-powered single dose, single-use autoinjector with audible user instructions for injecting of epinephrine, which is indicated for treating severe allergic reactions.

In France, Sanofi is proceeding with its Biolaunch project, which is designed to convert its chemical production facilities to biotechnology-based ones. The project includes a plan for a production facility for monoclonal antibodies at its site in Vitry-sur-Seine, which is expected to be completed by 2012, plus further investments to create a new biosynthetic process at its sites in Elbeuf and Vertolaye to improve corticosteroid production competitiveness.

Sanofi has several projects in emerging markets. In China, the company is expanding its manufacturing facility in Beijing by installing assembly and packaging lines for SoloStar, a prefilled injection pen used to administer the company's Lantus insulin product. In Hangzhou, China, Sanofi is building a new manufacturing site, scheduled to be completed in 2012, to replace an existing manufacturing facility there. In Russia, Sanofi is increasing insulin capacity at its facility in Orel; the company obtained the facility following its acquisition of a controlling stake in the pharmaceutical company Bioton Vostok in 2010. In Latin America, Sanofi is expanding its vaccine-manufacturing operations in Mirador, Argentina.

Sanofi has made several acquisitions to increase its presence in emerging markets. The company gained industrial sites from its 2009 acquisitions of generic-drug companies Zentiva in Eastern Europe and Medley in Brazil. In August 2010, sanofi also acquired Nepentes, a Polish manufacturer of pharmaceuticals and dermocosmetics. In October 2010, Sanofi acquired a 60% equity interest in the Chinese consumer-healthcare company Hangzhou Sanofi Minsheng Consumer Healthcare in partnership with Minsheng Pharmaceutical. Sanofi also acquired the Chinese specialty pharmaceutical company BMP Sunstone earlier this year.

In its vaccines business, Sanofi has made several key investments during

the past several years: the construction of a research facility in Toronto, Canada; the creation of a new vaccines campus in Neuville, France; the construction of bulk and filling facilities in Val de Reuil, France, and the establishment of a bacteriological bulk facility in Marcy l'Étoile, France; the creation of two new influenza vaccine facilities in Shenzhen, China, and Ocoyoacac, Mexico; and the completion of bulk and filling facilities, mainly dedicated to influenza and meningitis vaccines, in Swiftwater, Pennsylvania.

In April 2011, Sanofi completed its $20.1-billion acquisition of the biopharmaceutical company Genzyme and gained several manufacturing facilities. In its 2010 SEC annual filing, Genzyme reported on the construction of a new manufacturing facility in Framingham, Massachusetts, which is to include four bioreactors for producing Cerezyme (miglucerase) and Fabrazyme (agalsidase beta), which had been manufactured at the company's facility in Allston Landing, Massachusetts. According to Genzyme's annual filing, it expects to receive US approval for the Framingham facility in the second half of 2011. Genyzme had transferred production of certain products following manufacturing problems at the Allston facility and a subsequent FDA consent decree.

In 2010, Genzyme transferred its fill–finish operations for Fabrazyme and Myozyme (alglucosidase alfa), 160-L, sold in the US from the Allston facility to a contract manufacturer and to Genzyme's Waterford, Ireland, facility. Genzyme is expanding its fill-finish capacity by 400% at the Waterford facility, where Cerezyme, Lumizyme (alglucosidase alfa), and Myozyme (alglucosidase alfa) are filled–finished. It expects to receive product-specific approval for this additional capacity beginning in late 2011.

The company manufactures Lumizyme and Myozyme at the 4000-L bioreactor scale at a facility in Geel, Belgium. In its annual filing, Genzyme reported that it is adding a third 4000-L liter bioreactor at the facility and expects to receive approval of the additional capacity by the end of 2011. In addition, Genzyme began construction of an additional manufacturing facility in Geel, which will include two 4000-L bioreactors for Lumizyme and Myozyme production and expects to receive approval for this new facility in late 2014.

GlaxoSmithKline. GlaxoSmithKline (GSK) is moving ahead with a global restructuring program that is on track to deliver a target of £2.2 billion ($3.6 billion) of annual savings by 2012. These savings have been extracted from GSK's developed-country sales and marketing structure, support functions, R&D, and manufacturing infrastructure. Along with these changes are increased investment in emerging markets, according to the company's 2010 annual filing.

In emerging markets, in June 2011, GSK agreed to acquire Shenzhen Neptunus Interlong Bio-Technique's stake in the companies' previously formed joint venture, Shenzhen GSK–Neptunus Biologicals, for $39 million. The joint venture

develops and manufactures seasonal and pandemic influenza vaccines in China, Hong Kong, and Macau. In December 2010, GSK agreed to acquire the Chinese pharmaceutical company, Nanjing Mei-Rui Pharma, including a manufacturing facility in Nanjing City, Jiangsu Province, China. In Russia, GSK formed an alliance with JSC Binnopharm for the local secondary manufacture of several GSK vaccines. Under this alliance, which was announced in November 2010, GSK will supply bulk vaccine and provide technology and expertise to enable Binnopharm to undertake the secondary manufacture, including filling and packaging of GSK vaccines. Binnopharm will be responsible for gaining approval of their facilities to allow supply of GSK cervical cancer, rotavirus, and pneumococcal vaccines under Binnopharm's trademark for the Russian public market.

In biologics, in September 2010, GSK and the Swiss custom manufacturing organization Lonza formed an agreement under which Lonza will supply manufacturing capacity for five GSK early-stage monoclonal antibodies. Lonza will initially manufacture clinical-trial batches of five compounds currently in Phase I and II development and provide flexible capacity for late-stage development and commercial launch. As part of the agreement, GSK will work with Lonza to assess options for the design, specification, location, and construction of a biopharmaceutical manufacturing facility within the United Kingdom.

Also, in 2010, GSK sold its Cidra, Puerto Rico, facility after the plant's closure in 2009, which followed manufacturing problems and a subsequent FDA consent decree for the facility in the early 2000s.

Novartis. In November 2010, Novartis defined the company's strategic focus to include pharmaceuticals, eye care, Sandoz (the company's generic-drug business), consumer healthcare, vaccines, and diagnostics. In addition, Novartis plans to strengthen its commercial position in emerging markets in China, Russia, Brazil, and India.

As part of its emerging-market strategy, in June 2011, Novartis broke ground for a new, $140-million pharmaceutical manufacturing plant in St. Petersburg, Russia. Once completed and approved for commercial production, which is expected in 2014, the facility will produce approximately 1.5 billion oral solid dosage units per year. The facility is part of a $500-million, five-year investment into Russian healthcare infrastructure announced by Novartis in December 2010, which addresses three core areas: local manufacturing, R&D collaborations, and public-health development.

In late 2009, Novartis announced a $1-billion, five-year investment to expand the China Novartis Institute for Biomedical Research. In March 2011, Novartis completed the $125-million acquisition of an 85% stake in the Chinese vaccines company Zhejiang Tianyuan Bio-Pharmaceutical. Novartis also is constructing a new, $300-million vaccine-manufacturing facility in Goiana, Brazil. The technical startup of the facility is planned for the end of 2014.

In Western Europe and the US, Novartis is proceeding with a long-term redevelopment of its headquarters site in Basel, Switzerland. First begun in 2001, the goal of the project, called "Campus," is to invest in R&D, corporate, and administrative activities at the site and to transfer production facilities from the site to other sites in the Basel region. Through Dec. 31, 2010, the total amount spent on the project was $1.9 billion, and the company expects to spend a total of $2.6 billion through 2015. In October 2010, Novartis announced that it would invest $600 million during the next five years to build new laboratory and office space in Cambridge, Massachusetts.

In vaccines, Novartis is investing in a new $240-million rabies and tick-borne encephalitis vaccine-manufacturing facility in Marburg, Germany. The facility is expected to open in 2012. In late 2009, Novartis opened a large-scale influenza cell-culture vaccine and adjuvant manufacturing facility in Holly Springs, North Carolina, in partnership with the US Department of Health and Human Services, Biomedical Research and Development Authority. The total investment in the new facility is expected to be at least $900 million, partly supported by grants from the US government and previous investments in influenza cell-culture technologies at the Novartis vaccines site in Marburg.

As part of an effort to optimize its manufacturing footprint, Novartis divested a Sandoz site in Jena, Germany, and announced its exit from a Ciba Vision production site in Cidra, Puerto Rico. In April 2011, Novartis finalized its acquisition of the eye-care company Alcon.

Merck. Following its $49.6-billion acquisition of Schering-Plough in late 2009, Merck & Co. began a global restructuring program in February 2010, in which Merck announced plans to reduce its total workforce, measured at the time of the merger, by approximately 17% as well as to eliminate vacant positions at the time of the merger. The reduction comes from eliminating duplicative positions in sales, administrative, and headquarter organizations as well as from the sale or closure of certain manufacturing and R&D sites.

As part of that restructuring, Merck announced plans to phase out operations at certain research and manufacturing sites as well as to continue to consolidate office facilities worldwide, as outlined in the company's 2010 SEC annual filing. The eight research sites affected include those in: Montreal; Boxmeer (Nobilon facility only), Oss, and Schaijk, Netherlands; Odense, Denmark; Waltrop, Germany; Newhouse, United Kingdom; and Cambridge (Kendall Square), Massachusetts.

In the second half of 2010, Merck began phasing out operations at eight manufacturing facilities, and these sites will exit the global network as activities are transferred to other locations. Merck reported plans to cease manufacturing activities at its facilities in Comazzo, Italy; Cacem, Portugal; Azcapotzalco, and Coyoacan, Mexico; and Santo Amaro, Brazil, and the company intends to sell the Mirador, Argentina and Miami Lakes, Florida, facilities. In Singapore, chemical manufacturing will be phased out at the legacy Merck site, but it will continue at the legacy Schering-Plough site. The company's pharmaceutical

manufacturing operations will continue at both Singapore facilities. In addition, manufacturing operations at the Kenilworth, New Jersey, site will be discontinued, and these activities will be consolidated with existing operations at other Merck facilities. Also, earlier this year, Merck sold its contract biologics manufacturing activities to Fujifilm, including its equity interests in two Merck subsidiaries, Diosynth RTP and MSD Biologics UK. These entities had facilities in Research Triangle Park, North Carolina, and Billingham, United Kingdom.

In emerging markets, in July 2011, Merck signed a framework agreement with China's Simcere Pharmaceutical Group to form a joint venture in China with the goal of building a strategic partnership in development, registration, manufacturing, and sales. The initial focus of the partnership will be branded pharmaceutical products for cardiovascular and metabolic diseases. Simcere has seven GMP-approved manufacturing facilities in the Chinese provinces of Jiangsu, Hainan, Shandong, Jilin, and Anhui, according to company information. In April 2011, Merck formed a joint venture with India's Sun Pharmaceutical to develop, manufacture, and commercialize new combinations and formulations of branded generic drugs in emerging markets. Sun has 20 plants (for producing drug substances and finished products) in India, Israel, the US, Canada, Hungary, Brazil, Mexico, and Bangladesh.

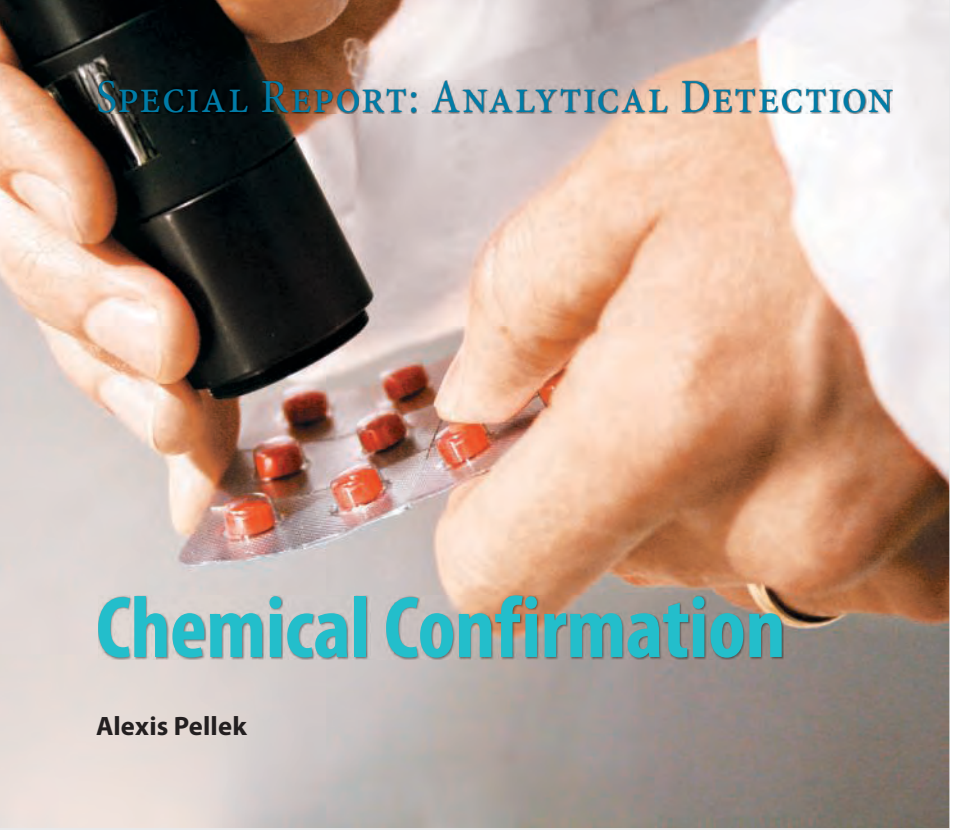
Roche. In November 2010, Roche announced a company-wide restructuring plan that is designed to result in annual cost savings of CHF 2.4 billion ($3.0 billion). Implementation, which is scheduled for 2011 and 2012, includes plans for reducing its workforce by 4800 positions worldwide. Most of the planned job reductions will occur in Roche's pharmaceuticals division, particularly in global sales and marketing organization and in manufacturing.

To further improve capacity utilization within its global manufacturing network, some technical operations activities will be reorganized in California, the US, Mannheim, Germany, and various other sites. In addition, Roche intends to seek buyers for its sites in Florence, South Carolina, and Boulder, Colorado. In its diagnostics group, Roche plans to close its manufacturing site in Graz, Austria, and transfer development and manufacturing activities relating to blood gas diagnostics to Rotkreuz, Switzerland, where the division's professional diagnostics unit has its global headquarters. Diagnostics chemical manufacturing and analytical services are expected to be discontinued in Mannheim, Germany, and transferred to Penzberg, Germany.

Roche will discontinue certain activities in research and early development. These include RNA interference research in Kulmbach, Germany, Nutley, New Jersey, and Madison, Wisconsin. In addition, plans also include reorganizing certain internal functions to free up resources for upcoming Phase II studies of new molecular entities.

Bristol-Myers Squibb. Bristol-Myers Squibb has substantially completed its new, $750-million multiproduct bulk biologics manufacturing facility in Devens, Massachusetts. The company plans to submit the site for regulatory approval in late 2011 or 2012, according to the company's 2010 SEC annual filling. The investment in the new biologics facility represents the largest capital project in the company's history. BMS also reported on meeting its goal of realizing its $2.5-billion productivity transformation initiative, first announced in December 2007, which included reductions to its manufacturing operations.

Other companies. Among other changes in Big Pharma manufacturing networks includes AstraZeneca's construction of a new $150-million manufacturing facility in the Kaluga region in Russia. In June 2011, the company also announced plans to establish a Predictive Science Center in St. Petersburg. In addition, AstraZeneca has established several partnerships with Russian development institutes, including the Skolkovo Innovation Centre and Russia Venture Company. In China, Eli Lilly is building a second manufacturing plant and dedicated diabetes research center. Earlier this year, Boehringer Ingelheim acquired the rights and substantially all the assets at Amgen's Fremont, California, development and manufacturing facility. The Fremont site includes a 100,000-ft^2 manufacturing facility with a pilot plant and process-development laboratories. Boehringer Ingelheim will use the facility to enhance its contract-manufacturing activities. The company has been a contract manufacturer for Amgen. **PT**



Chemical Confirmation

Alexis Pellek

Analytical detection techniques help manufacturers combat counterfeit drugs.

Alexis Pellek is the custom digital content manager for the pharmaceutical group of Advanstar Communications and is a regular contributor to *Pharmaceutical Technology*.

Pharmaceutical manufacturers can choose from a variety of anticounterfeiting technologies to deal with the ever-growing problem of counterfeit drugs in the supply chain. FDA and industry experts recommend a layered approach to protecting the integrity of the supply chain, which combines technologies for antitampering, serialization, and authentication (in the form of overt, covert, or forensic features) applied to the packaging or dosage form. Analytical detection methods can confirm the authenticity of a drug product by using technologies such as portable spectrometer-based readers that authenticate in the field, thin-layer chromatography kits that quickly verify the presence and amount of active pharmaceutical ingredient (API), or analytical laboratory screening services that offer extensive testing of packaging and finished dosage forms for counterfeits.

On-dose protection

TruTag Technologies in Honolulu developed an anticounterfeiting solution in the form of a covert silica microtag that is edible, economical, heat resistant, and can be mixed into a coating, dye, or ink. The microtag is encoded with a spectral pattern chosen from a library of up to a trillion unique patterns, Peter Wong, chief operating officer of TruTag Technologies, explains. "Therefore, our microtag is like a covert, 'edible barcode' and is as flexible a business tool as a traditional printed barcode," he says. The company's product was recently recognized as a promising new technology for anticounterfeiting by winning "Most Likely to Succeed" in the life sciences category at the Launch: Silicon Valley 2011 competition, an event focused on identifying emerging technology startups.

The microtags, which can be applied to a solid dosage form or to packaging components, are authenticated using a portable spectrometer-based optical reader. Wong says the company has received "quite a bit of interest" in applying the microtags to bulk API and are open to testing with an interested partner. TruTag's portable readers can confirm the authenticity of the product through a clear blister pack, so the product does not have to be destroyed. The microtags can also link to additional information stored in a manufacturer's database, such as e-Pedigree and track-and-trace systems.

Wong says that in the company's development work, the application of the microtags has been relatively straightforward. TruTag was able to combine small quantities of microtags with a tablet-coating mix, which was then sprayed onto solid oral dosage forms using standard industry pan coaters. Because silica (silicon dioxide) is a generally-recognized-as-safe (GRAS) material, says Wong, under the framework of FDA's draft guidance, *Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting* (1), the agency's filing process may be as simple as including the addition of TruTag microtags as an annual reportable change if the product already had silica as an ingredient, or require a CBE-30 supplement if silica is a new ingredient to the product.

Handheld spectrometers

Thermo Fisher Scientific in Wilmington, MA, offers several lightweight, handheld spectrometers designed to rapidly verify the identity of both raw materials and finished products. The company's TruScan and TruScan RM analyzers are based on Raman spectroscopy, and the microP-

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Pharmaceutical companies and regulatory agencies use the devices to verify raw materials and finished products, according to Duane Sword, senior director of strategic growth of Thermo Fisher Scientific's portable optical analysis business. "This method provides a more significant deterrent to counterfeiters since security measures based on packaging are often easily replicated by counterfeiters, whereas imitating the exact chemical formulation of a product is extremely difficult (and not cost-effective for counterfeiters)," he says.

Advanced analytical services

Another way that a drugmaker can identify counterfeits in the supply chain is by using the services of an analytical laboratory. Manufacturers send a sample of suspected product for testing, and the medication and the packaging can be analyzed.

Using Intertek's nuclear magnetic resonance spectroscopy (NMR) services, for example, can determine whether the API is present, and if present, at what levels. These results can show whether the sample is "a genuine attempt to make a copy or simply a mock product with no intent to contain an active ingredient," says Phil Norman, vice-president of Intertek Chemicals and Pharmaceuticals Division, based in Manchester, UK. This information, says Norman, can indicate the sophistication of the counterfeit and also helps the drug manufacturer make important decisions relating to public safety. "The investigation can also reveal if the packaging is not consistent with the reference product and potentially provide a rapid option for screening out counterfeits from the marketplace," he says.

Sample investigation uses a range of analytical detection technologies, such as spectroscopy (NMR, Fourier transform infrared, NIR, and Raman); liquid chromatography–mass spectrometry; gas chromatography–mass spectrometry; and microscopy, depending on what is the best approach for the manufacturer's specific problem. This type of advanced screening is typically used in specialized cases where a high level of detailed analysis is required, Norman says. "These laboratory investigative techniques are not an alternative to portable analytical detection devices, rather they offer options for clients who require that further, more detailed step, in obtaining data to confirm that a sample is counterfeit," he says.

Examples of these situations, he says, include cases where authorities have seized product as it is imported into a country, as well as where non-governmental organizations have sourced medicines from online pharmacies as part of their own investigations, which show a high proportion of counterfeits. "It is concerning to observe that a proportion of samples arriving at Intertek laboratories for investigation have come from legitimate supply chains," he says.

Conclusion

Counterfeiters are hard at work finding ways to replicate, trick, mimic, and dodge each new technology that stands in their way. Drug companies must continue to fight back with constant vigilance and new security methods to protect the pharmaceutical supply.

"The rising number of counterfeit drugs reaching even legitimate distribution channels coupled with the increasing sophistication of these copies, means that reliable and advanced analytical detection is a key part of a drug manufacturer's overall strategy to combat this problem," Norman says.

Combining anticounterfeiting measures designed to prevent counterfeits from reaching consumers such as anti-tamper packaging and overt authentication features, a robust serialization system, and technologies that detect the presence of adulterated and substandard medicines, drug manufacturers can work to protect their supply chains, brands, and customers.

Reference

1. FDA, *Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting* (Rockville, MD, July 2009). **PT**

Detection of counterfeits in developing countries

One solution for detecting counterfeit pharmaceuticals in developing countries is the use of thin-layer chromatography (TLC) methods. The World Health Organization estimates that potentially more than 30% of pharmaceuticals in developing nations could be counterfeit. Portable TLC kits are economical, do not require extensive training for use, and allow for rapid screening of product in the field (1). An example of such a portable laboratory is the GPHF-Minilab, which was developed by the Global Pharma Health Fund (GPHF), a charitable organization funded by Merck KGaA.

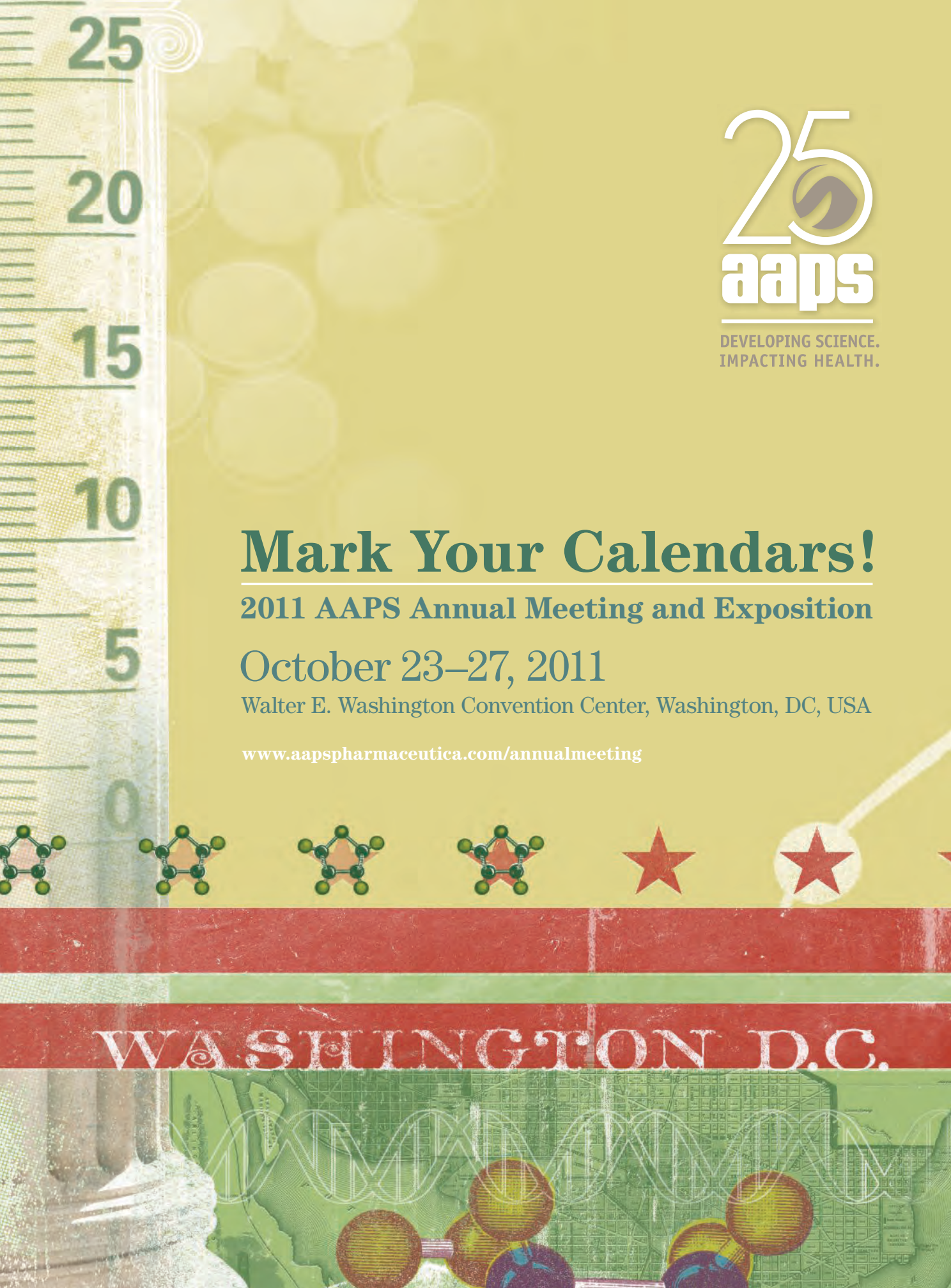
Thomas P. Layloff, PhD, senior quality assurance advisor for the Supply Chain Management System, part of the President's Emergency Plan for AIDS Relief, explains the advantages of TLC in protecting consumers from counterfeit pharmaceuticals. "The use of TLC to determine whether the right drug is present in approximately the right amount is very widespread because of ease of application, sustainability, low cost and very minimal support infrastructure required. For example, more than 300 GPHF TLC-based Minilabs have been sold and put in use all over the world. The Minilab technology requires no laboratory facilities or electricity; detection is based on visual comparisons. Since the TLC plates are single use, there is no maintenance of the chromatographic media."

Other technologies, he says, are more expensive and require more training but are also more accurate. A limitation of TLC, for example, is that "cogeners of the parent drug cannot be discerned by the technology, but fortunately these types of counterfeit products are expensive to manufacture and they occur in the high-cost markets such as the United States," he says. "The TLC stands out for speed and cost but there is a tradeoff in the ability to detect sophisticated counterfeit products."

To read the full Q&A with Layloff, see the expanded version of this sidebar on PharmTech.com.

Source

1. J. Sherma, *Acta Chromatographica*, **19**, 5–20 (2007).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Improving API Synthesis

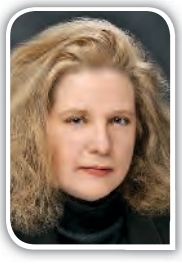
Patricia Van Arnum

O-arylation and *O*-alkylation, a one-pot protein synthesis, a combined approach in continued processing and chemocatalysis, and green-chemistry applications are the targets of some recent advances in API synthesis.

Organic chemists face the ongoing challenge of developing and optimizing a synthesis for active pharmaceutical ingredients (APIs). These challenges involve a multitude of issues designed to improve yield, purity, stereoselectivity, process conditions (i.e., temperature and pressure), scalability, and production economics. A recent literature review reveals insight into some of these challenges as they relate to organic chemical production overall and pharmaceutical chemical development in particular.

O-arylation and *O*-alkylation

Researchers at Merck & Co. recently reported on a large-scale synthesis of a potent glucokinase inhibitor, MK-0941, through selective *O*-arylation and *O*-alkylation. Glucokinase inhibitors are under clinical development for treating Type II diabetes. MK-0941 is a glucokinase inhibitor that has a differentially substituted 3,5-dihydroxybenzamide structure, and an efficient synthesis that would be suitable for large-scale preparation was required. The researchers reported on several drawbacks of the early-stage synthesis, including multiple recrystallizations to improve enantomeric purity, yield variability, and batch-to-batch variability in the impurity profile of the desired compound. Several factors were key to improving the synthesis: a highly selective mono-*O*-arylation of methyl 3,5-dihydroxybenzoate with 2-ethanesulfonyl-5-chloropyridine and the selection of a proper protective group for the S_N2 *O*-alkylation (1).



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One-pot protein synthesis

Researchers at the University of Chicago recently developed a one-pot protein synthesis involving a 204-residue covalent-dimer vascular endothelial growth factor (VEGF). VEGF is a protein involved in vasculogenesis and angiogenesis and is studied in reference to pharmaceutical compounds, particularly anticancer compounds. The researchers reported that they prepared a 204-residue covalent dimmer VEGF with full mitogenic activity from three unprotected peptide segments by one-pot native chemical ligations. The covalent structure of the synthetic VEGF was confirmed through mass measurements, and the three-dimensional structure of the synthetic protein was determined by high-resolution X-ray crystallography (2, 3).

Chemical protein synthesis is one research area of University of Chicago professor Stephen B.H. Kent, a co-author of the recently published research on the VEGF synthesis. One area of focus is the preparation of long polypeptide chains of protein molecules by the chemoselective reaction (i.e. chemical ligation) of unprotected protein segments containing mutually reactive functional groups. An example of these ligation chemistries is thioester-mediated, amide-forming ligation or native ligation. The resulting polypeptide chains are folded with good efficiency to produce high-purity synthetic proteins. The covalent structure of the molecule is confirmed by mass spectrometry, and the three-dimensional fold structure of the synthetic protein is determined by X-ray crystallography. Another area of research focus is kinetically controlled ligation, a chemistry used for the full convergent synthesis of large protein molecules. The research group is examining insertion reactions for creating molecular diversity in preformed molecular scaffolds and the use of polymer-supported ligation.

Suzuki-Miyaura cross couplings in a continuous flow system

Researchers at the Massachusetts Institute of Technology (MIT) reported on the development of a Suzuki–

IMAGE: STOCKBYTE / GETTY IMAGES

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Miyaura cross-coupling reaction in a continuous-flow microreactor system. Specifically, the researchers reported on a continuous-flow Suzuki–Miyaura cross-coupling reaction that started from phenols and produced various biaryls in good yield using a microfluidic-extraction operation and a packed-bed reactor. The project used a multidisciplinary approach with the research on microreactor technology developed by a team led by Klaus F. Jensen, department head, Warren K. Lewis professor of chemical engineering, and professor of materials science and engineering at MIT. The organic synthesis portion of the project was developed by a group led by Stephen Buchwald, Camille Dreyfus professor of chemistry at MIT (4, 5).

Suzuki coupling is a palladium-catalyzed coupling between organoboron compounds and organohalides and is an important reaction in organic chemistry in general and in the development of pharmaceutical compounds specifically. Akira Suzuki, distinguished professor emeritus at Hokkaido University in Sapporo, Japan, was a corecipient of the 2010 Nobel Prize in Chemistry for the development of palladium-catalyzed cross coupling (6).

Although batch manufacturing is the predominant form of manufacturing in the pharmaceutical industry, there is growing interest in microreactor technology. In general, microstructured devices with small internal volumes and high surface-to-volume ratios offer transport capabilities for rapid mixing, enhanced heat transfer for good temperature control, and intensified mass transfer. Microstructured devices operate in continuous-flow environment, which can offer certain advantages, such as controlled process conditions, high flow rates, and high mass throughput. Continuous operations also may allow bulk-chemistry processes to have high production capacities. Fluid dynamics determine the characteristics of continuous-flow equipment such as pressure loss, residence time, heat-transfer characteristics, and mixing time (7).

Buchwald is engaged in various research projects involving catalysis, including the creation and study of new ligands, the design of new methods to form carbon–nitrogen bonds through the use of metal catalysts, such as palladium or copper, new methods for the formation of carbon–carbon bonds, including asymmetric transformations, as well as continuous flow chemistry using microreactors and capillary tubing. Buchwald recently reported on the continuous-flow synthesis of 3,3-disubstituted oxindoles by a palladium-catalyzed α-arylation/alkylation sequence. Specifically, he reported on the pallidum-catalyzed α-arylation of oxindoles in continuous flow involving a biphasic system, a precatalyst, and a packed-bed microreactor. The reaction was integrated into a two-step continuous-flow sequence for rapid, modular, and efficient syntheses of 3,3-disubstituted oxindoles (8).

Jensen's research is focused on understanding and controlling the interaction of reaction and transport processes in realizing and testing functional microstructured and nanostructured materials and devices for chemical, biological, optical, electronic, and energy applications, including the use of microfabricated systems. He recently reported on research using an automated microfluidic system for online optimization in chemical synthesis. He reported that the time and material required for an optimization trial were minimized by performing reactions in an integrated silicon microreactor and incorporating high-performance liquid chromatography for in-line monitoring of the reaction performance. The system was used to optimize two different reactions to understand the potential impact of the system for reaction development. The two reactions studied were a Knoevenagel condensation reaction and a mulitparameter optimization to maximize the yield of benzaldehyde in the oxidation pathway of benzyl alcohol to benzaldehyde to benzoic acid (9).

In other work, Jensen's team reported on the design and use of a high-pressure and high-temperature microsystem. Key parameters for the fabrication of the microreactors and modular fluidic packaging were to withstand high pressure and temperature conditions (i.e., 30MPa and 400 °C). The researchers reported on various applications of the high-pressure/high-temperature plug and play microsystems. These applications included multiphase follow visualization through the transition of liquid–liquid immiscible hexane–water segmented flow to homogeneous supercritical flow, on-chip supercritical water oxidation, and synthesis of iron oxide nanoparticles (10).

Green-chemistry applications

Green chemistry is an important tool in improving reactions, which may for example, improve production economics through reduced energy requirements, lower solvent use, fewer byproducts, and less waste generation. Bruce H. Lipshutz, professor in the chemistry and biochemistry department at the University of California at Santa Barbara, was recognized in June with a Presidential Green Chemistry Challenge Award, an annual recognition by the US Environmental Protection Agency for advances in green chemistry (11).

Nanodispersed surfactant. Lipshutz was recognized for designing a second-generation surfactant, TPGS-750-M, which can be used in industrial processes to replace large amounts of organic solvents with small amounts of the surfactant nanodispersed in water only. TPGS-750-M is composed of tocopherol (i.e., vitamin E), succinic acid, and methoxy polyethylene glycol. TPGS-750-M forms nanomicelles in water that are lipophilic on the interior and hydrophilic on the exterior. A small amount of TPGS-750-M may be used to spontaneously form 50–100-nm diameter micelles in water to serve as nanoreactors. The particle size of TPGS-750-M is engineered to facilitate organic reactions, such as cross-couplings. Reactants and catalysts dissolve in the micelles, resulting in high concentrations that lead to increased reaction rates at ambient temperature (11).

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Several common organic reactions that are catalyzed by transition metals can take place within TPGS-750-M micelles in water at room temperature and in high isolated yields. These reactions include ruthenium-catalyzed olefin metatheses (Grubbs), palladium-catalyzed cross-couplings (Suzuki, Heck, and Sonogashira), unsymmetrical aminations, allylic aminations and silylations, and aryl borylations. The technology also offers the potential for palladium-catalyzed aromatic carbon–hydrogen bond activation for carbon–carbon bond formation at room temperature. In its awards recognition, EPA cited other advantages to the technology: straightforward product isolation; elimination of frothing and foaming commonly associated with other surfactants; efficient recycling of the surfactant after use; recovery of the insoluble product by extraction; and reuse of the aqueous surfactant with negligible loss of activity. Future generations of surfactants may include a catalyst tethered to a surfactant to provide both the reaction vessel (i.e., the inside of the micelle) and the catalyst to enable the reaction (11).

Flow processing. Eli Lilly submitted two entries to EPA's Green Chemistry Presidential Challenge. The first involved the commercial production of LY2624803*H3PO4, an investigational new drug candidate in Phase II clinical trials and a drug acquired by Lilly with its acquisition of Hypnion. The original synthesis was not amenable to large-scale manufacture and had several environmental and safety issues with the original chemistry. Among them were: dimethylformamide/sodium hydride in step one of the synthesis; methylene in various steps; a molten step with observed self-heating; an aldehyde purification that would be unsafe at increased scale; phosphoryl chloride in large excess; and chromatographic purification (11).

The company made several improvements to the synthesis using flow processing. An efficient carbonylation replaced an inefficient oxidation catalyzed by tetramethyl pentahydropyridine oxide. Hydrogen replaced sodium triacetoxyborohydride in a reductive amination. Although both operations required high pressure (i.e., 1000 psi), which would be difficult to manage in a batch environment, both operations were amenable to flow processing (11).

Green chemisty equates to good process chemistry.

Process mass intensity (PMI), a measure of the efficiency of a synthesis, was improved. PMI is the total mass of raw materials (including water) put into a process for every kilogram of product produced. The original route had a PMI of more than 1000 before chromatography. The new route has a net PMI of 59, representing a 94% reduction in PMI and a 96% percent reduction with chromatography. Lilly implemented its new route for LY2624803*H_3PO_4 on a pilot-plant scale in Indianapolis, Indiana, during 2009 and on a commercial scale in Kinsale, Ireland, during 2010, according to the EPA report (11).

Improved Grignard chemistry. Another entry from Eli Lilly involved the development of Grignard chemistry using a continuous stirred tank reactor. The Grignard reaction is applied to many industrial reactions, including producing intermediates for pharmaceutical compounds. Some commercial-scale problems with the reaction, however, are strongly exothermic activation and reaction steps, heterogeneous reactions with potential problems suspending and mixing the reaction mixture, and operational hazards posed by ethereal solvents, such as diethyl ether (11).

Eli Lilly developed inherently safer Grignard chemistry using a continuous stirred tank reactor that allowed continuous formation of Grignard reagents with continuous coupling and quenching. This approach minimized hazards by operating at a small reaction volume, performed metal activation only once during each campaign, and used 2-methyltetrahydrofuran (MeTHF). MeTHF offers certain advantages, such as that it may be derived from renewable resources and may provide improved chemoselectivity and stereoselectivity compared with Grignard products using other ethereal solvents. The continuous approach provided reductions of 43% in metal use, 10% in Grignard reagent stoichiometry, and 30% in PMI (11) According to the EPA report, Lilly is using the continuous stirred tank reactor Grignard approach to produce two key materials: the penultimate intermediate of LY2216684*HCl, a norepinephrine reuptake inhibitor currently under clinical investigation, and for an intermediate for another drug under clinical development. Commercial production on a 22-L scale is under consideration (11).

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Nick Toltl, PhD
R&D Manager, SGS Life Science Services, Canada

For questions contact Jamie Carpenter at jcarpenter@advanstar.com

Controlled Crystallization During Freeze-Drying

A Process Suitable for Large-Scale Production of Drug Nanocrystals

Hans de Waard, Niels Grasmeijer, Wouter L.J. Hinrichs, Thomas De Beer, and Henderik W. Frijlink

The authors discuss the preparation of lipophilic drug nanocrystals by controlled crystallization during freeze-drying. In-line Raman spectroscopy was used to monitor the crystallization of the drug during freeze-drying to elucidate how the size of the drug crystals could be controlled. A three-way nozzle was used to create a spray freeze-drying process suitable for large-scale production.

Hans de Waard* is postdoctoral researcher, **Niels Grasmeijer** is a doctoral student, **Wouter L.J. Hinrichs** is senior researcher, and **Professor Henderik W. Frijlink** is chairman, all at the Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands, tel. +31 50 363 2397, fax +31 50 363 2500, h.de.waard@rug.nl. **Professor Thomas De Beer** is a professor in the Laboratory of Pharmaceutical Process Analytical Technology at the Department of Pharmaceutical Analysis, Ghent University.

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Modern drug-discovery techniques are rapidly increasing the number of lipophilic drugs (1). This lipophilicity and consequent slow dissolution rate results in poor bioavailability after oral administration. However, these drugs are easily absorbed from the gastrointestinal tract once dissolved (2). Therefore, the bioavailabilities of these drugs can be improved by increasing dissolution rate (3).

The formation of drug nanocrystals is one of many strategies to increase dissolution rate. Drug nanocrystals are crystalline drug particles with a diameter below 1 μm. Because of their small size, the saturation concentration around these particles is increased (Ostwald–Freundlich, see Eq. 1), the boundary layer thickness is decreased (Prandtl, see Eq. 2), and the specific surface area is increased (4). All these effects contribute to an increased dissolution rate (Noyes–Whitney, see Eq. 3) as shown below (5).

$$C_{s,curved} = C_{s,flat} \cdot \exp\left(\frac{2\gamma_s M_d}{RT\rho_d r}\right) \quad \text{(Eq. 1)}$$

where, $C_{s,curved}$ is the saturation concentration around the curved surface, $C_{s,flat}$ is the saturation concentration at a flat surface, γ_s is the interfacial surface tension, M_d is the molecular weight of the drug, R is the gas constant, T is the temperature, ρ_d is the density of the drug, and r is the radius of curvature of the drug.

$$h = \frac{k \cdot \sqrt{L}}{\sqrt{V}} \quad \text{(Eq. 2)}$$

where, h is the hydrodynamic boundary layer thickness, k is a constant, L is the length of the surface in the direction of the flow, and V is the relative velocity of the flowing liquid versus the flat surface.

$$\frac{dm}{dt} = \frac{d \cdot A}{h}(C_s - C) \quad \text{(Eq. 3)}$$

where, dm/dt is the dissolution rate of the drug, d is the diffusion constant, A is the specific surface area, and C is the concentration in the bulk.

Current methods to prepare drug nanocrystals can be divided into bottom-up and top-down methods. Top-down methods (e.g., ball milling and high pressure homogenization) have disadvantages, such as the use of surfactants, low process yields, and the difficulty in achieving uniform-size distribution (6, 7). Bottom-up methods are generally precipitation-based but also have disadvantages, such as difficulty in controlling crystal size and the need to use toxic organic solvents.

To overcome these disadvantages, controlled crystallization during freeze-drying (CCDF) was developed as a novel method to prepare drug nanocrystals (8). First, two solutions are prepared: lipophilic drug in tertiary butyl alcohol (TBA), and matrix material in water. The two solutions are mixed and immediately frozen. The temperature in the freeze-dryer is then increased to −25 °C and this temperature is kept constant for a few hours. Finally, the frozen mixture is freeze dried at this relatively high temperature.

Because the mixture of drug, matrix material, TBA, and water is thermodynamically unstable, the drug and matrix material can either crystallize upon freezing or after the temperature in the freeze-dryer is increased (9). Therefore, the first aim of the study was to elucidate when the four different components crystallized during the production process by placing a Raman probe in the freeze-dryer above the sample. By using this in-line analytical tool, the crystallization of the individual components was monitored.

The second aim of the study was to modify the freeze-drying process to ensure its suitability for large-scale production. Because the thermodynamically unstable mixture must be frozen immediately after mixing, at laboratory-scale, only small quantities were mixed in glass vials and subsequently frozen on a freeze-dryer shelf or by immersion in liquid nitrogen. At production scale, it is difficult to mix and freeze large quantities sufficiently fast, so a three-way nozzle was evaluated for its ability to solve this technical problem. The three-way nozzle used in this study allows two liquids to flow separately through the nozzle; the two solutions are mixed just outside the nozzle by an atomizing airflow from a third channel and sprayed into liquid nitrogen, thus achieving high freezing rates. To investigate whether this three-way nozzle could modify the small batch freeze-drying process into a semicontinuous spray freeze-drying process, the crystallinity, particle size, and dissolution rate of the obtained products were determined.

Table I: Composition of the different solutions used to prepare controlled crystallized dispersions. The mannitol–water solution and fenofibrate–tertiary butyl alcohol (TBA) solution were mixed in a 6:4 ratio.

Before lyophilization		After lyophilization	Freezing technique
$C_{mannitol}$/ water (mg/mL)	$C_{fenofibrate}$/ TBA (mg/mL)	Drug Load (% w/w)	
25	39	30	Vial immersed in liquid nitrogen
25	39	30	Spraying of droplets into liquid nitrogen
31	25	35	Vial on a precooled freeze-dryer shelf
25	25	40	Vial immersed in liquid nitrogen
25	25	40	Spraying of droplets into liquid nitrogen

Materials and methods

Raw materials. Fenofibrate and TBA were obtained from Sigma-Aldrich Chemie, mannitol (the matrix material) was obtained from Roquette and VWR International.

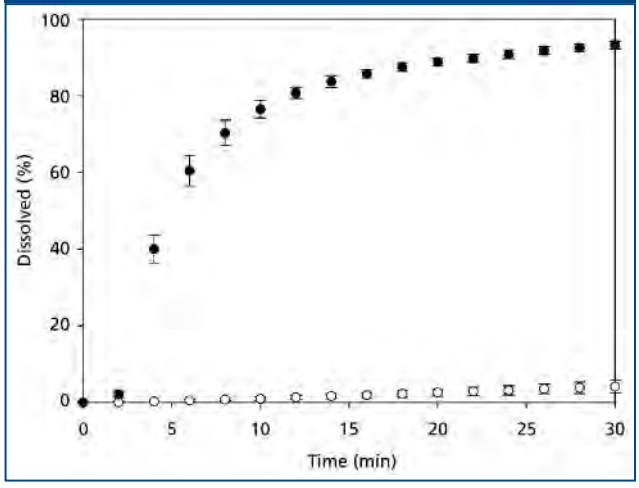
Preparation of the controlled crystallized dispersions by freeze-drying. To prepare the controlled crystallized dispersions, fenofibrate was dissolved in TBA and mannitol (the matrix material) was dissolved in water (see Table I for compositions). For the small batch freeze-drying process, the aqueous solution and the TBA solution were mixed in a 6:4 ratio.

The mixture was frozen in vials on a precooled (−50 °C) freeze-dryer shelf (Christ) or by immersion in liquid nitrogen after being placed on the precooled freeze-dryer shelf. The temperature of the samples was equilibrated at −50 °C on the freeze-dryer shelf. The temperature of the freeze-dryer shelf was then increased to −25 °C. This temperature was kept constant for at least three hours, after which time the samples were dried at the same temperature by decreasing pressure and using a condenser temperature of −85 °C.

Preparation of the controlled crystallized dispersions by spray freeze-drying. For the semicontinuous spray freeze-drying process, the aqueous solution and the TBA solution were pumped separately (9 and 6 mL/min, respectively) through the three-way nozzle and sprayed into liquid nitrogen. After the nitrogen was evaporated, the frozen sample was placed on the freeze-dryer shelf and equilibrated at −50 °C. The temperature was gradually increased to −25 °C and kept constant for three hours. After this, the samples were dried at the same temperature by decreasing the pressure and using a condenser temperature of −85 °C.

In-line Raman spectroscopy. A noncontact probe (Kaiser Optical Systems) was placed immediately above the sample in the freeze-dryer and coupled via a glass fiber optic cable to a Raman Rxn1 spectrometer (Kaiser Optical Systems) equipped with an air-cooled charge-coupled device (CCD) detector (back-illuminated deep depletion design). The laser

Figure 1: Dissolution profiles of tablets composed of a physical mixture (open symbols) and controlled crystallized dispersions (black symbols) of 35% w/w fenofibrate in mannitol. (n = 3–6; mean ± standard deviation).



wavelength was the 785-nm line from a 785 Invictus near infrared (NIR) diode laser. All spectra were recorded at a resolution of 4 cm^{-1} using a laser power of 400 mW. The HoloREACT reaction analysis (Kaiser Optical Systems) and profiling software package, the Matlab Software package (version 6.5, MathWorks), and the Grams/AIPLSplusIQ software package (version 7.02, Thermo Scientific) were used for data collection, transfer, and analysis. Spectra were preprocessed by baseline correction using Pearson's method. Spectra were collected every minute during freeze-drying, and the exposure time was 30 s.

Scanning electron microscopy (SEM). SEM pictures were taken with a JEOL JSM 6301-F microscope (JEOL) using an acceleration voltage of 5 kV. The samples were dispersed on top of double-sided sticky carbon tape on metal disks and coated with a thin layer of gold–palladium in a Balzers 120B sputtering device (Balzers Union).

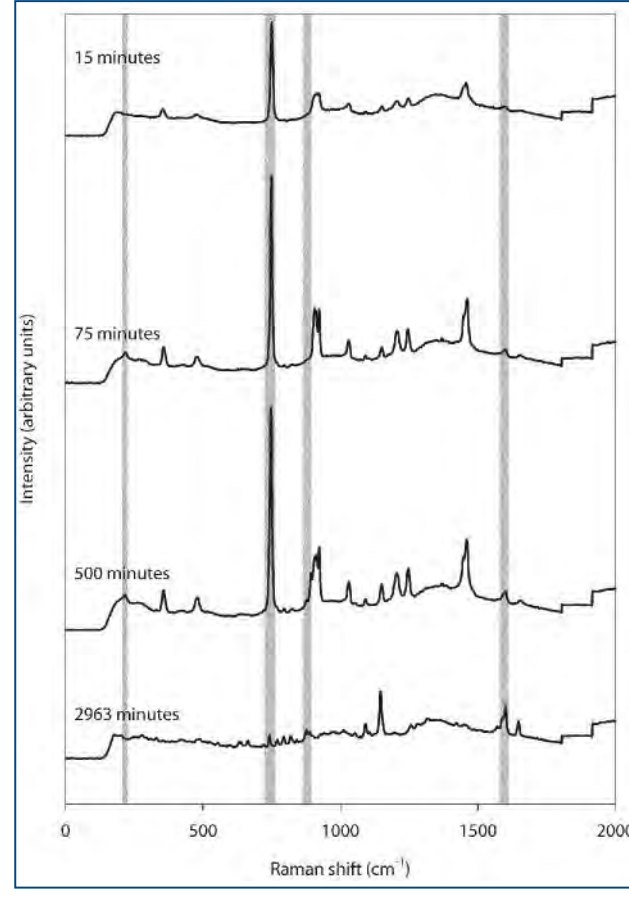
Tableting. Tablets of 100 mg were prepared on an ESH compaction apparatus (Hydro Mooi) at a compaction rate of 5 kN/s to a maximum compaction load of 5 kN. The tablets were stored for at least one day in a vacuum desiccator over silica gel before further processing.

Dissolution. The dissolution rate of fenofibrate from the tablets was tested in 1 L of 0.5% w/v sodium dodecyl sulfate solution (Fagron) at 37 °C in a *USP* dissolution apparatus II (Rowa Techniek) with a paddle speed of 100 rpm. The concentration of fenofibrate was determined spectrophotometrically by a UV–Vis spectrophotometer (UV-1601, Shimadzu) at a wavelength of 290 nm.

Results and discussion

In-line Raman spectroscopy. The dissolution rate of the solid dispersion, which had been frozen on a precooled freeze-dryer shelf, was higher than the dissolution rate of the physical mixture (see Figure 1). Because the freeze-dried sample was fully crystalline (as determined by differential scanning calorimetry and X-ray powder diffraction, the difference in dissolution rate was likely caused by differences in drug crystal size. Therefore, the drug crystals in the controlled crystallized dispersion were smaller (probably in the nanosize range), than the drug crystals in the physical mixture (x50 = 13 μm, determined by laser diffraction).

Figure 2: Raman spectra during freeze-drying of the rapidly frozen sample during freezing (15 and 75 min), after the temperature was increased to −25 °C (500 min), and during drying (2963 min). The gray bars indicate the characteristic peaks of water (208–226 cm^{-1}), tertiary butyl alcohol (725–763 cm^{-1}), δ-mannitol (865–895 cm^{-1}), and fenofibrate (1580–1610 cm^{-1}).



Although both components in the solid dispersion were fully crystalline, it was not clear at what point during the process the drug and matrix material crystallized. Therefore, in-line Raman spectroscopy was used to measure crystallization during the freeze-drying procedure. The Raman spectra clearly show peaks corresponding to water (208–226 cm^{-1}), TBA (725–763 cm^{-1}), δ-mannitol (865–895 cm^{-1}), and fenofibrate (1580–1610 cm^{-1}).

These peaks are clearly separated from each other (see Figure 2), so the crystallization of the individual components could be monitored throughout the process. To determine

FIGURES 1-3,5 ARE COURTESY OF THE AUTHORS

Figure 3: Dissolution profiles of fenofibrate from tablets composed of physical mixtures (open symbols), dispersions prepared by the batch process (black symbols), and dispersions prepared by the semicontinuous process (gray symbols). The tablets contained 30% (circular symbols) and 40% (square symbols) w/w fenofibrate in mannitol. (n=3–6; mean).

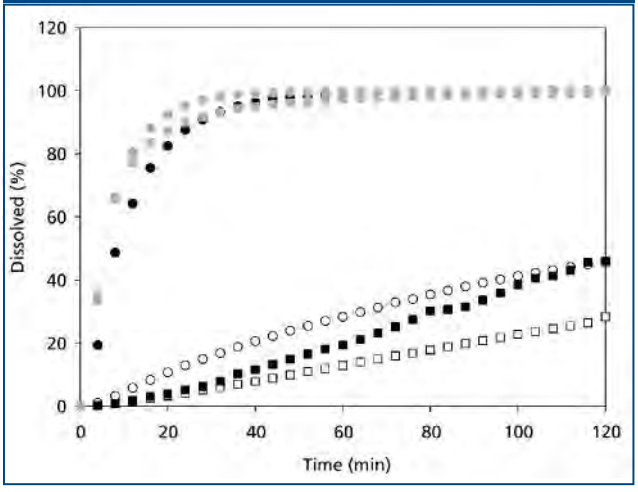
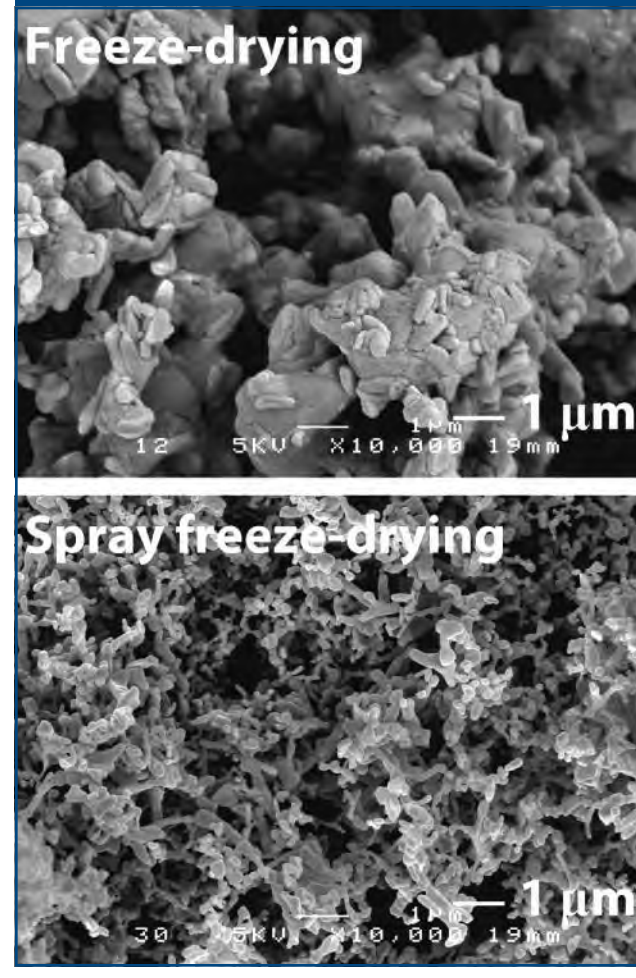


Figure 4: Scanning-electron microscopy pictures of controlled crystallized dispersions prepared by freeze-drying (top) and spray freeze-drying (bottom).



crystallization, the relative intensities of the individual peaks of fenofibrate, mannitol, and water were determined. An increase in the peak intensity indicates the formation of crystals of the corresponding component. Peak intensity cannot be used to determine crystallization of TBA because liquid TBA already shows a peak with a high intensity. Therefore, the width of this peak was used to determine the onset and end of crystallization (10). A narrowing of the peak indicates the start of the TBA crystallization.

After 15 min on a precooled freeze-dryer shelf, only the TBA peak can be seen in the Raman spectrum (see Figure 2). This indicates that at this stage of the process, the solvents were still in the liquid state and that the solutes were still dissolved in these solvents. After 75 min, the intensity of the peak corresponding to ice increased, and the width of the TBA peak decreased. However, no significant change in the relative intensities of either fenofibrate or mannitol peaks could be seen, which shows that during the freezing step, the solvents crystallized and that, importantly, the solutes did not. During equilibration at −50 °C the solutes still did not crystallize.

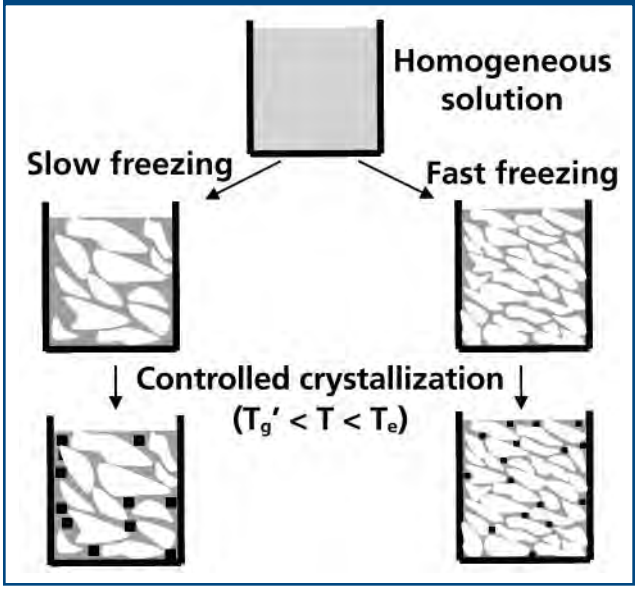
However, when the temperature was increased to −25 °C and maintained for 500 min, mannitol and fenofibrate peaks increased. This increase in intensity finished well before the drying step was initiated, indicating that crystalline mannitol and crystalline fenofibrate were formed during the crystallization step and that this crystallization was finished before drying started. To initiate drying, the pressure was decreased at 2963 min. The intensity of the water peak decreased and the width of the TBA peak increased thus indicating that sublimation of the solvents had begun. In summary, upon freezing, only the solvents crystallized, while the solutes did not crystallize until the temperature in the freeze-dryer was increased. Crystallization of the solutes finished before drying started.

From freeze-drying to spray freeze-drying using a three-way nozzle. Because only small quantities can be prepared in vials in the initial experiment, this freeze-drying process is not suitable for large-scale production. Therefore, a three-way nozzle was tested to determine if it could convert the small-batch freeze-drying process into a semicontinuous spray freeze-drying process for scale-up.

Solid dispersions prepared by freeze-drying (freezing in liquid nitrogen) and spray freeze-drying were compared. The dissolution rate of fenofibrate from dispersions prepared by the semicontinuous spray freeze-drying process was faster, especially at a higher drug load, than that of dispersions prepared by the small-batch freeze-drying process (see Figure 3).

Because dispersions obtained from the different processes were all fully crystalline, the differences in dissolution rate should be attributed to differences in drug crystal size. Indeed, the SEM pictures indicate that crystals obtained

Figure 5: A diagram of the controlled crystallization process. The white areas represent the solvent crystals, the grey areas the freeze concentrated fraction, and the black squares the drug nanocrystals.



from the semicontinuous process were smaller than those obtained from the batch process (see Figure 4). However, in-line Raman spectroscopy measurements showed that the solutes did not crystallize upon freezing, but after the temperature of the freeze-dryer shelf was increased.

Therefore, the difference in drug crystal size can be explained by the difference in freezing rate (11). During the batch process, vials containing 2 mL solution were immersed in liquid nitrogen, whereas during the semi-continuous process very small droplets were sprayed into liquid nitrogen. Because the volumes of the individual droplets were smaller than the volume of liquid in the vial, rapid freezing rates could be achieved by spray-freezing into liquid nitrogen (12).

A higher freezing rate leads to the formation of smaller solvent crystals, and therefore smaller interstitial spaces (containing the freeze-concentrated fraction) between the solvent crystals (13). Because the drug and matrix crystallize in the freeze-concentrated fraction, the size of the drug crystals is limited to the size of these interstitial spaces. Thus, when smaller interstitial spaces are formed, the final drug crystal size is smaller (see Figure 5).

Conclusion

By using in-line Raman spectroscopy, it was shown that during the freezing step of the CCDF process only the solvents crystallized. The solutes did not crystallize until the temperature in the freeze-dryer was increased. Furthermore, the three-way nozzle can be used to alter the small-batch process into a semicontinuous process that is suitable for large-scale production. Controlled crystallized dispersions prepared by the semicontinuous process results in even smaller nanocrystals due to a higher freezing rate. Therefore, the semicontinuous process is not only suitable for large-scale production, but can also result in a better product.

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Understanding Fluidized-Bed Granulation

Using In-Line Particle-Size Measurements

A. Burggraeve, T. Van Den Kerkhof, M. Hellings, J.P. Remon, C. Vervaet, and T. De Beer

The authors incorporated a particle-size analyzer into a laboratory-scale top-spray fluid-bed granulator to monitor granule size distribution (GSD) continuously during granulation. A two-level full-factorial design was used to study the influence of several process and formulation variables on the end-product GSD, measured in-line with spatial-filter velocimetry (SFV). The results demonstrated the beneficial use of an SFV particle-size analyzer during granulation. The tool was sensitive to particle-size changes and increased process understanding.

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The pharmaceutical industry has used fluid-bed granulation extensively for several decades to improve powder properties (e.g., flowability and compressibility) for downstream processing. During this two-phase process that includes spraying and drying, the addition of a binder liquid causes primary particles to aggregate and form granules (1). The granule size distribution (GSD) is of major importance to the final quality of the granulated product because it influences density, flowability, and dustiness. Hence, the understanding and control of granule growth during manufacturing are of major importance to the delivery of a high-quality end product.

Sieve analysis, image analysis, and laser diffraction are common off-line particle-size determination techniques. These methods are usually time-consuming and labor-intensive because they require sample preparation. In recent years, interest in real-time process analysis has increased, partly because of FDA's process analytical technology (PAT) initiative. Several studies have examined at-line, on-line, and in-line particle-size analysers. The application of image analysis, near-infrared spectroscopy, acoustic-emission spectroscopy, focused-beam reflectance spectroscopy, and spatial-filter velocimetry for real-time granulation monitoring has been investigated (2–24).

The authors applied spatial-filter velocimetry (SFV) in-line during top-spray fluid-bed granulation to obtain GSD information continuously. During SFV measurements, particles pass through a laser beam, and the corresponding shadow thrown onto the detector helps determine the chord-length distribution of the measured particles. The measurement zone at the probe tip is equipped with sapphire windows that are kept clean by an internal compressed-air supply system, thus preventing window fouling. A two-level full-factorial design was used to examine the influence of process and formulation variables on end product GSD, measured in-line with SFV and compared with off-line laser diffraction (LD) results. The granule-size data obtained continuously in-line were analyzed in detail to improve understanding of the influence of the examined process and formulation variables on the granule growth mechanism. Furthermore, the in-line quantified GSD was related to the off-line-measured tapped density using univariate,

Figure 1: Average D50 results obtained with spatial-filter velocimetry (SFV) and laser diffraction (LD) for all design-of-experiments batches.

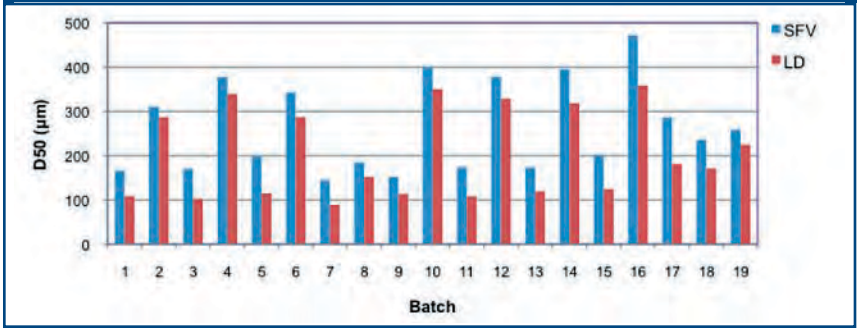

Table I: Lower and upper levels of the examined process and formulation variables.

Variable	Unit	Lower level	Upper level
Hydroxypropyl methylcellulose	%w/w	1	3
Tween 20	%w/w	0.2	0.3
Inlet air T during spraying	°C	40	50
Inlet air T during drying	°C	50	70

multivariate, and multiway models, thus allowing early estimation of this end-product property during granulation.

Materials and methods

Materials. The dry powder mass consisted of dextrose monohydrate (700 g, Roquette Frères) and unmodified maize starch (Cargill Benelux). This was granulated with an aqueous binder solution of hydroxypropyl methylcellulose (HPMC, type 2910, 15 mPa, Dow Chemical) and Tween 20 (Croda Chemicals Europe). The amounts of HPMC and Tween 20 were varied according to the design of experiments (DOE, see Table I). The HPMC binder was always sprayed as a 4% solution, and the total amount of solids was kept constant at 1 kg by varying the amount of maize starch accordingly.

Fluid-bed granulation set-up. Granulations were performed in a laboratory-scale fluid-bed granulator (GPCG 1, Glatt). An SFV probe (Parsum IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik) was installed in the fluid-bed granulator at a height of 200 mm above the distributor plate and at approximately 50 mm from the side wall of the granulator. Granules passed through a 4-mm aperture, and an internal and external air connection prevented fouling of the measurement zone and ensured the dispersion of the powder mass. SFV data were collected every second during the entire granulation processes, but an average granule-size distribution was saved every 10 s. The granulation process finished when an outlet air temperature of 37 °C and a product temperature of 45 °C were reached.

DOE. A two-level full-factorial design was applied to study the effects of HPMC concentration, Tween 20 concentration, inlet-air temperature during spraying, and inlet-air temperature during drying (see Table I) on the end-product's GSD. Three design center point repetitions were performed (i.e., 19 experiments in total).

Off-line granule characterization. For each DOE granulation experiment, the end-product particle-size distribution was determined with LD (Mastersizer S long bench, Malvern Instruments). Average D10, D50, and D90 values were determined based on three measurements of each batch.

End-product tapped-density measurements (1250 taps, J. Englesmann) were performed in triplicate, and the average tapped density was used.

Results and discussion

Comparison of in-line SFV and off-line LD particle-size measurements. The GSD of the end products measured in-line using SFV was compared with the off-line determined LD granule sizes for all DOE batches. Although SFV and LD are based on different measurement principles (LD assumes spherical particles, whereas SFV does not), similar GSDs were expected. Figure 1 displays the average D50 values measured with SFV (i.e., the average of the last granulation minute, or six data points) and LD for the end granules of all 19 DOE batches. Similar D50 differences between the 19 experiments were obtained by the two particle-sizing techniques. However, D50 sizes measured with LD were always lower than those obtained by SFV. The same observations were made for the D10 and D90 values.

The authors believe that this difference in GSD is caused by the LD measurement technique. The quantified particles experience rapid accelerations as the air stream passes through a venturi. The high shear applied during this process and the subsequent collisions with the wall of the apparatus may cause granules to break or crumble. Pressurized air also disperses the granules during the SFV measurements, but the particles pass directly through the measurement zone. No collisions occur because high shear is not applied. The authors' hypothesis was confirmed by the GSD measurement of low-friability spherical granules (i.e., Cellets 100, 200, and 350, Pharmatrans Sanaq Pharmaceuticals) using SFV and LD under software and experimental settings identical to those for the DOE granules. The LD measurements did not systematically underestimate the GSD, in contrast to observations obtained for the breakable granules. An additional explanation for the discrepancy between SFV and LD values might be found in the assumption of a spherical shape during LD measurements.

Size segregation during fluidization should also be addressed because it influences in-line SFV measurements (23). Inappropriate fluidization can cause a high amount of larger granules to be present in the lower part of the chamber and a high amount of smaller granules to appear in the upper part of the chamber. The SFV probe is placed in the upper part of the chamber, which the largest particles cannot reach under low inlet airflow rates, potentially resulting in an underestimation of granule size. Figures 2a and 2b display the difference between SFV and LD D50 results for

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the 19 DOE batches, arranged according to increasing SFV end-granule size and LD end-granule size in the *x* axes, respectively. Because these differences did not increase as a function of increasing end granule size, the authors concluded that no size segregation had occurred.

These primary results suggest that although a systematic difference exists between LD and SFV data, the SFV technique can successfully measure the actual particle-size distribution during granulation.

Improved process understanding through continuously gathered GSD information. The average D50 values, obtained from the in-line SFV measurements during the last minute of granulation, were used as DOE responses. The experimental results revealed three significant DOE variables. HPMC concentration, inlet air temperature during drying, and the interaction between these factors had a positive effect on the D50 values. Because GSD information was obtained every 10 s through in-line SFV measurements, the authors took a closer look at the individual granule-size profiles of several DOE batches to better understand the significance of the studied DOE factors.

Influence of the HPMC concentration. The distinctive particle-size trajectory during fluid-bed granulation consisting of three phases can be distinguished clearly in Figure 3. Between the first captured granule-size data and time point 1, the particle size remains constant, which corresponds to the mixing phase. Between time points 1 and 2, the granule size increases because of the agglomeration of powder particles. The drying period is depicted after time point 2. The graph reveals that the positive effect of the HPMC concentration on granule size was caused by the following two factors:

- Large amounts of HPMC resulted in large particles throughout the spraying period. At time point 2 (see Figure 3), Batch 13 (1% HPMC) had an average granule size of 200 µm, while Batch 14 (3% HPMC) displayed an average granule size of 415 µm.
- Large amounts of HPMC created less friable granules, which resulted in less fines during the drying period. Between time points 2 and 3 (see Figure 3), Batch 13 (1% HPMC) showed ap-

Figure 2a: Differences between average D50 values measured with spatial-filter velocimetry (SFV) and laser diffraction (LD), arranged according to increasing SFV particle size.

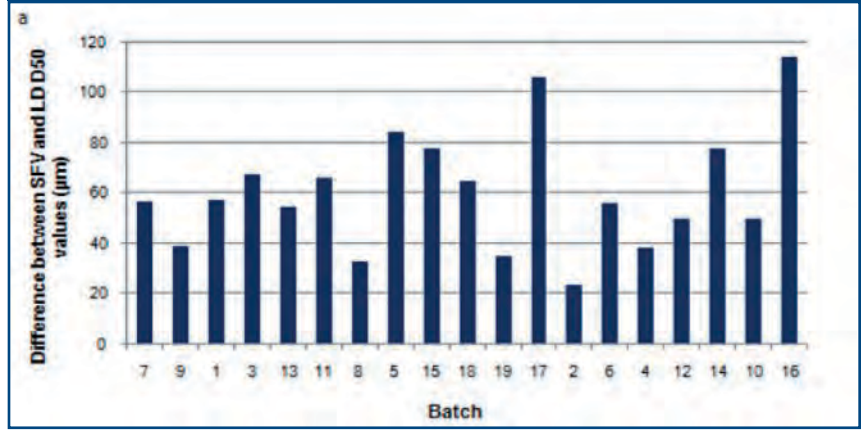


Figure 2b: Differences between average D50 values measured with spatial-filter velocimetry (SFV) and laser diffraction (LD), arranged according to increasing LD particle size.

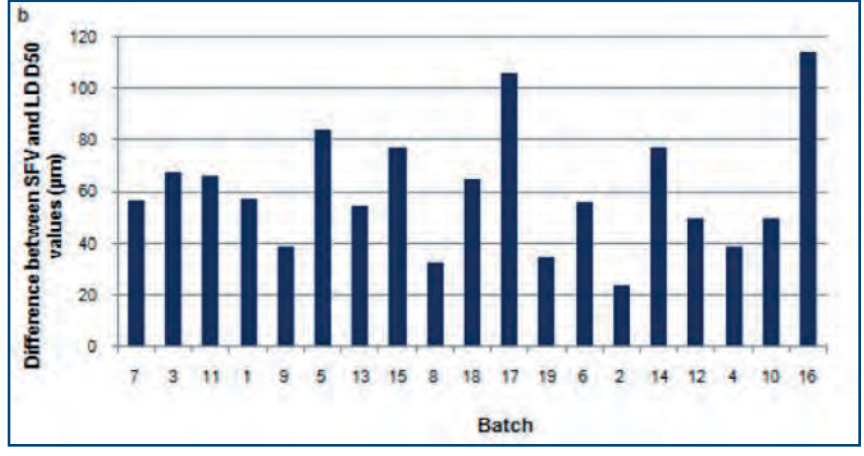


Figure 3: D50 profile of batches 13 and 14 (1%/3% hydroxypropyl methylcellulose, 0,2% Tween 20, 50 °C spraying *T*, 70 °C drying *T*) at (1) the beginning of the spraying phase, (2) the end of the spraying phase, and (3) the end of the drying period.

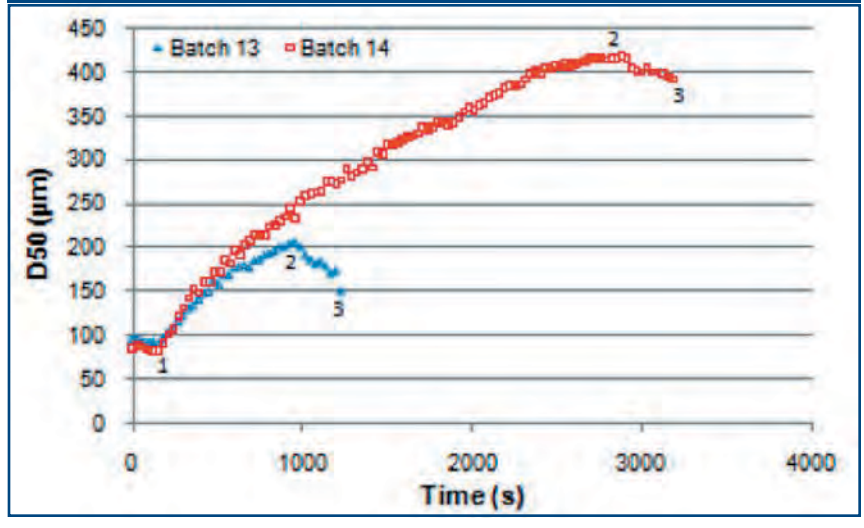
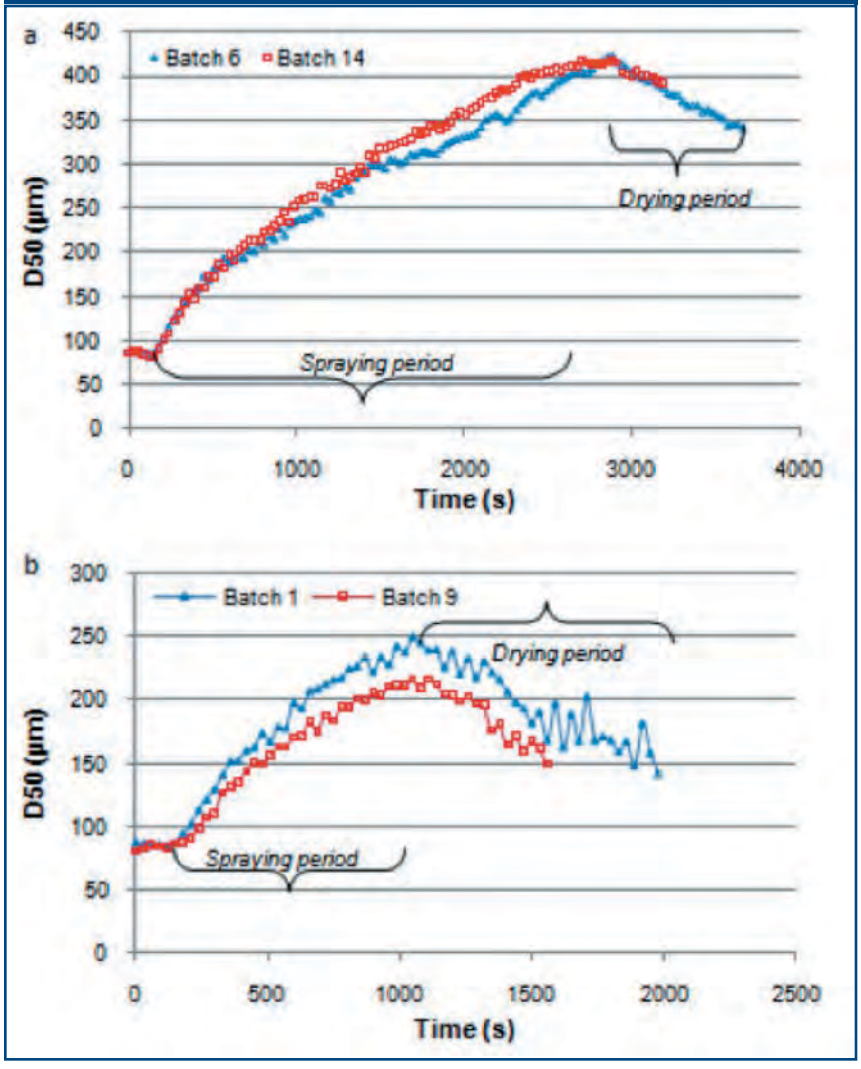


Figure 4: D50 profile of (a) batches 6 and 14 (3% hydroxypropyl methylcellulose [HPMC], 0.2% Tween 20, 50 °C spraying *T*, 50 °C, and 70 °C drying *T*) and (b) batches 1 and 9 (1% HPMC, 0.2% Tween 20, 40 °C spraying *T*, 50 °C, and 70 °C drying *T*).



proximately a 60-µm average decrease in granule size, while the granule size of Batch 14 (3% HPMC) decreased by only 25 µm.

Influence of the inlet air temperature during the drying period. DOE analysis showed that the drying inlet air temperature was of less importance (statistical significance $p < 0.05$) to the GSD than the HPMC concentration (statistical significance $p < 0.001$). An explanation can be found in Figure 4. Figure 4a displays the in-line measured D50 profiles of Batches 6 (50 °C drying temperature) and 14 (70 °C drying temperature). The other settings were the same for both batches. These batches showed a similar granule-size trajectory throughout the spraying phase. During the subsequent drying period, Batch 6 yielded smaller end-sized granules because of higher levels of attrition during a longer drying phase.

Figure 4b displays the granule-size data of two other batches with different drying conditions. Batch 1 was dried at 50 °C, and Batch 9 at 70 °C. Both batches had identical initial process conditions, but a different granule growth profile occurred during the spraying period. Although the difference in drying temperature between the two batches caused a clear difference in particle-size evolution during the drying period (i.e., a larger decrease in particle size at the lower temperature of Batch 1), the end granule sizes used for the DOE analysis were similar. Hence, for these batches, a similar response value was used in the DOE analysis, despite the fact that the batches showed different granulation trajectories. This result might explain why the drying temperature was of limited significance according to the DOE. Only through the information obtained continuously in-line from the SFV probe was it possible to develop this in-depth understanding.

Influence of the inlet air temperature during the spraying period. Figure 5 shows the D50 data obtained in-line during the spraying period of two batches manufactured at different spraying temperatures. During the agglomeration phase of Batch 5 (spraying temperature of 50 °C), a higher fluctuation in granule size was observed, compared with Batch 1 (spraying temperature of 40 °C). This result was caused by the continuous entrapment of small particles in and subsequent discharge from the filter bags. At the higher temperature, small particles were present for a longer period of time than they were in Batch 1 because the faster evaporation of binder liquid led to slower agglomeration. However, at the end of the spraying periods, a similar particle size was observed at both temperatures. Although the detailed profile of granule growth through in-line granule-size monitoring showed a difference in agglomeration kinetics, the different spraying temperature did not create a difference in granule size at the end of the spraying period.

Estimation of granule tapped density from in-line SFV measurements. The tapped density of the end product is, like GSD, also important to further processing. Univariate, multivariate, and multiway approaches were considered to relate the in-line determined GSD to the tapped density of the 19 DOE batches (tapped density as dependent variable: 19 × 1 *Y*-vector). A univariate linear model was built using the D50 SFV values of the end granules of the 19 DOE batches as independent variables (19 × 1 *X*-vector). A multivariate partial least squares (PLS) model was built using the D01, D10, D25, D50, D63, D75, D90, and D99 SFV values of the end granules of the 19 DOE experiments as independent variables (19 × 8 *X*-matrix). A multiway *N*-way PLS (*N*-PLS)

model was built using the D01, D10, D25, D50, D63, D75, D90, and D99 SFV values of the 19 DOE experiments in a function of complete batch process time as independent variables (three-way *X*-matrix).

Table II compares the goodness of fit (R^2) and root mean square error of estimation (RMSEE) of the different models. The multivariate PLS tapped-density model had the highest R^2 value and the lowest RMSEE value. The low RMSEE of the model suggests the ability of the in-line SFV data to predict the off-line measured tapped density. Nevertheless, the model performance should be tested independently because the RMSEE value relates to the error within the calibration set and may overestimate the actual model performance.

Figure 5: D50 profile during the spraying period of batches 1 and 5 (1% hydroxypropyl methylcellulose, 0.2% Tween 20, 40 °C/50 °C spraying *T*, 50 °C drying *T*).

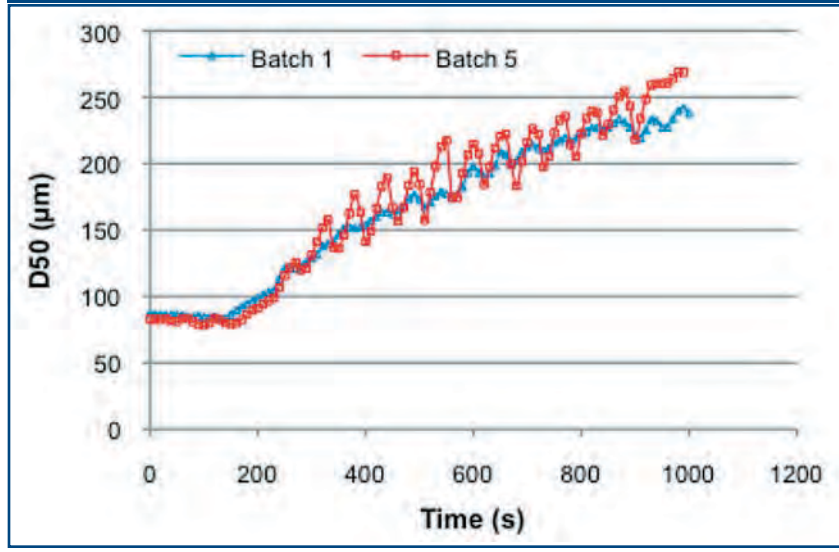


Table II: R^2 and RMSEE of univariate, multivariate, and multiway tapped-density models.

	Univarite		Multivariate (PLS)		Multiway (N-PLS)	
	R^2 (%)	RMSEE	R^2 (%)	RMSEE	R^2 (%)	RMSEE
Tapped density	69	0.0339	82	0.0279	70	0.0360

Note: RMSEE is root mean square error of estimation.

Conclusion

The results of this study show the feasibility of SFV for the real-time monitoring of GSD during fluid-bed granulation. The technique was sensitive to PS changes during the performed granulations and did not underestimate the granule size because of size segregation. Probe fouling did not occur. The continuously obtained GS information enabled a better understanding of the significance of the studied DOE factors on granulation. This understanding was not possible based on the off-line LD data of the end product. Finally, a multivariate PLS model was built to estimate end-product tapped density using continuously obtained GSD during granulation, which may improve batch-release time.

Next to real-time process monitoring of critical quality attributes, which helps to improve process understanding, another goal of PAT is to use the real-time critical information to steer or adjust the process toward its desired state based on feedback and feed-forward loops. Granule particle-size distribution and density are important granule quality attributes. In a future study, the authors aim to use in-line collected granule information gathered during the spraying phase to adjust process variables from the consecutive drying phase, hence guiding the drying process to the desired granule properties.

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Controlled Release from Porous Platforms

Spomenka Simovic, Dusan Losic, and Krasimir Vasilev

The authors present a method for controlling the release of therapeutics by applying a plasma polymer layer to the surface of porous materials. The current study applied this technique to the release of antibiotics and a protein. The approach substantially reduced the initial burst release and provided zero-order release kinetics. The method can be applied to any type of porous drug carrier because the techniques for depositing a polymer overlayer are independent of the substrate.

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Advances in nanoscience and nanotechnology have led to the development of novel drug-delivery platforms. During the past decade, attention has focused on nanoporous materials of which the pore size, pore distribution, geometry, and surface functionality can be controlled at the micro- and nanoscale (1–4). For example, porous alumina and porous titanium architectures obtained electrochemically have been proposed for implantable medical devices such as bone implants, vascular stents, and immunoisolation capsules (5–11). The interest in porous materials for therapeutic implants arises not only because of their ability to support tissue integration, but also because they can carry drugs (4, 6). The pores of these materials can be loaded with therapeutic agents and thus act as reservoirs for slow drug elution over extended periods of time, ranging from several days to several weeks (4, 6, 7). The advantages of local therapy through extended release time are high therapeutic concentrations at the target site and minimal systemic exposure (4, 7).

Porous aluminum has been used extensively as a scaffold for bone-tissue engineering applications. The biocompatibility of porous aluminum has been established, and the material has current clinical applications in orthopedic and dental implants (12). Also biocompatible, titanium and its alloys, particularly Ti-6Al-4V, have been used in orthopedic and dental implants extensively since the 1970s (13). It is estimated that more than 500,000 total joint replacements, primarily of hips and knees, and 100,000–300,000 dental implants are provided each year in the United States (13). About 25% of hip-replacement surgeries were undertaken to correct the failure of a previous implant. If an implant is improperly installed, loosening and osteolysis can occur. To overcome this problem, implant bone material should stimulate rapid bone regeneration to fill deficient bones and affix the implant firmly to the bone. The aim of the current research was to engineer bone implants that control and guide rapid healing (12, 13).

In 1994, two large trials demonstrated the superiority of coronary stents over conventional angioplasty in the treatment of coronary artery disease by showing 30% reductions of restenosis rates (14). However, such interventions are associated with major complications. For example, the prolifera-

tion of vascular smooth muscle cells (VSMC)can narrow the prosthesis, and endothelial-cell (EC) injury and dysfunction can result in thrombosis. A stent surface that incorporates titanium nanotubes can promote re-endothelialisation and decrease VSMC proliferation (8). Titanium nanotubes improve the proliferation and function of endothelial cells, decrease the proliferation of VSMCs, and enhance the production of prostaglandin I2, which mitigates thrombosis and restenosis (8).

To understand how endothelial cells interact with TiO_2 nanostructured surfaces (i.e., how nanotopography affects the morphology of ECs), scientists grew bovine aortic endothelial cells on nanotubular and flat surfaces (8). Cells on nanotubular substrates had elongated morphologies, but cells on the flat surfaces were spread out and covered greater surface areas. Because of the elongation, cells on nanotubes covered 60% of the average area occupied by the control cells. The elongated cells also had increased proliferation and extracellular matrix production when compared with their spread-out counterparts. In addition, elongated cells had higher migration speeds. Since migration into the wound site is a major mode of re-endothelialization, enhanced EC motility may greatly improve healing after injury or device implantation (8).

The encapsulation of living cells (i.e., cellular immunoisolation using semipermeable porous aluminum barriers) has also been investigated in the past several decades as a potential treatment for diseases such as Parkinson's, Alzheimer's and Type I diabetes (11). The encapsulation of living cells is a promising future therapy because immunoprotected cells, such as pancreatic islets or hepatocytes, can respond physiologically both *in vitro* and *in vivo* to appropriate stimuli (11).

Scientists have adopted two general strategies to control drug release rate from porous materials. The first strategy relies on the adjustment of pore diameter and pore depth to control drug loading and release (4). The second uses surface functionalization of the pores, which affects drug affinity, and consequently release kinetics (4). However, these strategies have drawbacks. For example, in both strategies, the release kinetics are marked with an initial burst that may not be desirable in some applications. In addition, reducing the pore diameter to extend the length of drug release leads to a reduced pore volume and, consequently, less drug can be stored (6, 7). This article introduces a novel strategy for controlling the release of therapeutics from porous materials and demonstrates its applicability using model antibiotics and a protein.

Experimental protocols

High-purity aluminum foil (99.99 wt %, Alfa Aesar) with a thickness of 100 μm was used to fabricate anodic aluminim oxide (AAO) substrates, according to the published method (15). Aluminum foil was degreased in acetone, sonicated for 30 min, thoroughly rinsed with MilliQ water, and electrochemically anodized using two-step anodization following previously reported procedures (16, 17). The first anodization was performed for 2–4 h under a 60–80 V and an electrolyte temperature of 1 °C in 0.3 M oxalic acid. After the resulting aluminum layer was dissolved, the second anodization was performed as described previously. The anodization conditions were maintained to ensure that all porous layers had the same pore diameters (70–90 nm) and pore thickness (20 μm).

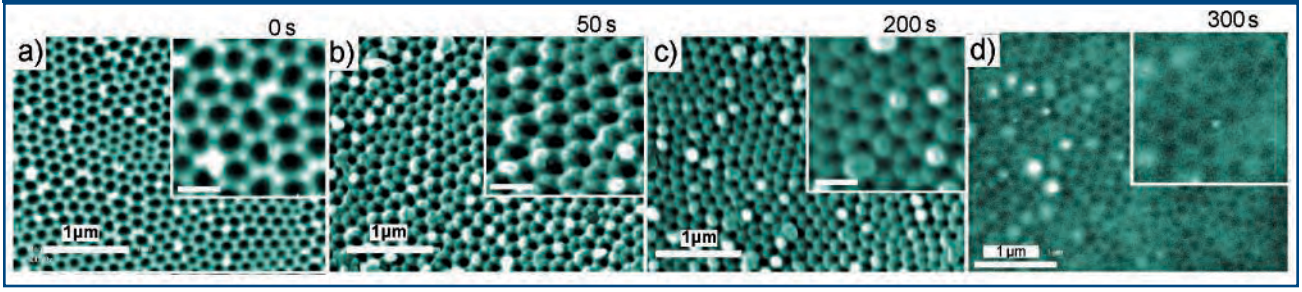
The drugs were loaded through consecutive deposition (20 times) followed by drying under vacuum for 2 h. Release testing was carried out in 5 mL of phosphate buffer (PB) at 37 °C. For each point in drug-release determination, 0.5 mL of medium was removed, diluted by 2.5 mL PB, and spectrophotometrically analyzed for drug content. Withdrawn medium was immediately replaced with 0.5 mL of fresh PB.

Plasma polymerization was carried out in a custom-built reactor described elsewhere using a commercial 13.56-MHz plasma generator (Advanced Energy, 16, 17). The depositions were carried out in an atmosphere of pure allylamine (AA) at a pressure of 0.22 Torr. An input power setting of 20 W was used in combination with a matching network to minimize reflected power. The deposition of AA under these conditions was carried out for 50, 200, and 300 s. The deposition rate was about 0.5 nm/s^{-1}, determined by ellipsometry on polished silicon wafers. Scanning electron microscopy (SEM) images were obtained on a Philips XL 30 FEGSEM.

Results and discussion

Controlling drug release from porous materials. To overcome the drawbacks of current approaches, a strategy for controlling drug release rate from porous materials was developed. The aim was to enable zero-order release kinetics with minimal burst release and without compromising the amount of loaded drug, which is important in long-term therapies (18). At the heart of this strategy is the deposition of a plasma-polymer layer with controlled thickness on top of the porous substratum loaded with a drug. The hypothesis was that the plasma-polymer layer would reduce the pore diameters at the surface, which, in turn, would define the rate of drug release form the pores. Plasma polymers are formed on a substrate from a gas phase when a selected precursor is electrically excited (19). Using plasma polymers for the present drug-delivery platform design has several advantages. Firstly, solvents are not involved because plasma polymers are deposited in the gas phase. Solvents may lead to loss or contamination of the loaded drug. Secondly, the thickness of the plasma polymer overlayer can be controlled with nanometer precision by the plasma-deposition conditions (in this particular study, by deposition time), which is important to establish precise control over release rate. Finally, in this study, plasma polymer films were deposited from vapor of allylamine, which resulted in films rich in amine functional groups. These types of films promote the adhesion and function of biological cells (20, 21).

Figure 1: Scanning electron microscope images of the anodic aluminim oxide (AAO) bare surface and (a) AAO modified with allylamine plasma polymer using deposition times of (b) 50 s, (c) 200 s, and (d) 300 s.



The authors chose AAO as a model porous platform because it can be prepared by a self-ordering anodization process using simple preparation procedures (15, 16, 20–21). It consists of an array of perpendicular and highly ordered pores with a diameter of 80 nm and a depth of 20 µm. To demonstrate control of drug release rate through this approach, the authors selected common antibiotics and a protein as model compounds of various molecular weights. These items include levofloxacin (MW 370), vankomycin (MW 1449), and bovine serum albumin (BSA, MW 66400). As a last step, an allylamine plasma-polymer film of predetermined thickness was deposited on top of the porous material loaded with drug. The thickness of the deposited film was controlled by the time of deposition, which was 50, 120, 200, and 300 s.

SEM characterization of the porous substrata after plasma-polymer deposition for 0, 50, 200, and 300 s is shown in Figure 1. After plasma deposition, pore diameters decreased from 80–90 nm to < 20 nm. The thickness of plasma-polymer films deposited from the same precursor on plain silicon wafers were measured by ellipsometry as 41 nm, 89 nm, 134 nm, and 200 nm when films were deposited for 50, 120, 200, and 300 s, respectively. However, the thickness measured on plain surfaces can only be used as a guide. Previous reports demonstrated that plasma polymers deposit differently on porous materials (20). Films grow from the rims of the pores and reduce the diameter of the pores at the surface. Importantly, the plasma polymers do not fill the pores, but only deposit at the pore entrance (16).

Drug-release kinetics: proof of concept. The drug-release profiles from AAO for samples with and without plasma-polymer film deposited on the surface are presented in Figures 2–4. Increasing the time of deposition (i.e., film thickness) clearly led to slower release for all three model drugs. Release behavior is also a function of drug type. Extended release of levofloxacin (see Figure 2) of three weeks can only be achieved if the plasma deposition time is prolonged to 500 s. In the case of vancomycin (see Figure 3), which has a molecular weight more than three times larger than that of levofloxacin, extended release can be achieved after plasma deposition of only 50 s. A clear correlation between time of deposition and drug release profiles was observed. From uncoated samples, drug is completely released within 45 min. Depositing plasma polymer for 50 s extends the release to about 200 h. Deposition for 200 s further extends the release because only 50% of drug is released after 500 h. Figure 4 shows the release of BSA. As in the case of antibiotics, increasing the time of deposition led to a slower release rate; release could be extended to six weeks when plasma polymer was deposited for 200 s.

The release kinetics from plasma-coated platforms can be described in two phases. The initial fast release within the first 45–60 min (see Figures 2–4) can be regarded as a burst, whereas release patterns from 1 h to completed release can be considered controlled release and fit into first- and zero-order models (see Table I, 20–21). The parameters show that zero-order kinetics best account for the experimental data. Furthermore, zero-order release (i.e., constant k_0) follows the same rank order as plasma-polymer deposition time. With increasing deposition time, the zero-order release constant decreases exponentially (see Table I). Zero-order release kinetics are a desirable release pattern because a constant amount of drug is released in each time interval (13). Such release kinetics, typical for reservoir transdermal delivery systems, are rarely reported for porous devices (15).

The ability to control the release rate of various drugs, including proteins, makes the authors' system a potential platform for the design of various therapeutic implants and drug-delivery devices. The results demonstrate that it is possible to achieve zero-order release kinetics from porous materials through controlled deposition of a plasma-polymer layer. The method for controlled drug release by deposition of a plasma polymer overlayer also could be extended to any type of porous drug carrier because the deposition techniques are independent of the substrate.

Conclusion

The authors described a method for controlled release of therapeutics from porous materials that has the potential to be applied to various therapeutics and types of porous

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Figure 2: The influence of plasma polymer coatings on the release profiles of levofloxacin. The legend shows plasma time depositions.

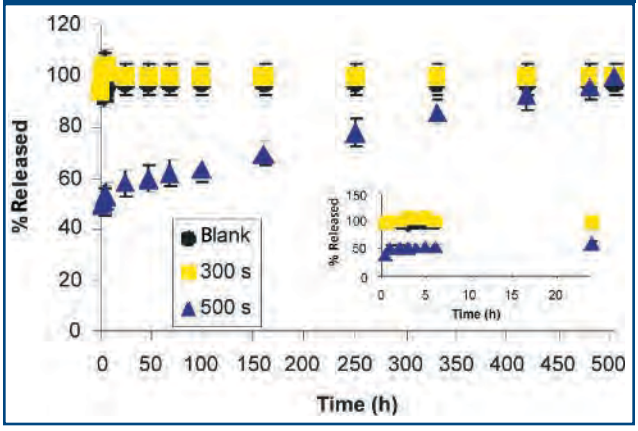

Figure 3: The influence of plasma-polymer coatings on the release profiles of vankomycin. The legend shows plasma time depositions.

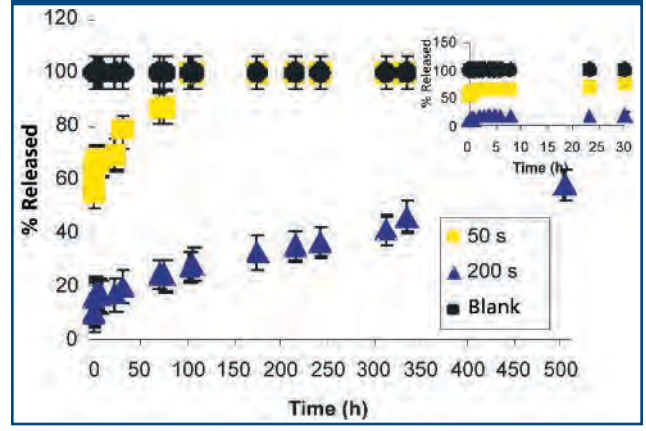

Figure 4: The influence of plasma-polymer coatings on the release profiles of bovine serum albumin. The legend shows plasma time depositions.

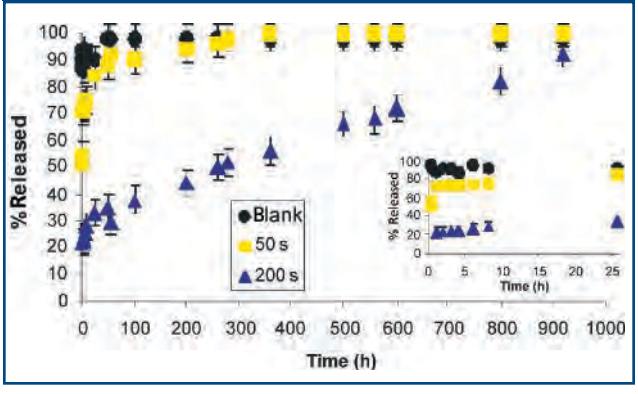

Table I: Controlled-release parameters for 1–500 h.

Plasma-polymer deposition time	First-order release		Zero-order release	
	r	$k_1 \times 103$ (h^{-1})	r	k_0 (h^{-1})
Levofloxacin				
500 s	0.98	0.45	0.99	0.65
Vankomycin				
50 s	0.97	4.1	0.98	0.33
200 s	0.94	3.1	0.99	0.085
Bovine serum albumin				
50 s	0.95	0.65	0.98	0.32
200 s	0.98	1.2	0.99	0.03

materials. The method involves the application of a plasma-polymer layer on top of porous materials, and the thickness of this layer controls release kinetics. Athough the current study emphasizes plasma polymerization as a tool to reduce pore diameter at the surface, future work should consider the influence of the plasma polymer's physical properties, such as hydrophilicity, on drug release. The ability of plasma polymerization to provide films of various physical and chemical properties provides enormous flexibility for fine tuning drug-release platforms to suit various drugs and applications.

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Functional Equivalence for Equipment Replacements

A Risk-Management Case Study (Part 2)

Ted Frank, Stephen Brooks, Kristin Murray, Steve Reich, Ed Sanchez, Brian Hasselbalch, Kwame Obeng, and Richard Creekmore

This case study on functional equivalence for equipment replacements is the second of eight in a series put together by the Product Quality Research Institute Manufacturing Technology Committee (PQRI–MTC) risk-management working group. The series is meant to advance the understanding and application of the International Conference on Harmonization (ICH) Q9 *Quality Risk Management* guideline by providing actual examples of risk-management assessments used by the bio/pharmceutical industry. The introductory article and first case study, on defining design space, appeared in the July 2011 issue of *Pharmaceutical Technology* (1).

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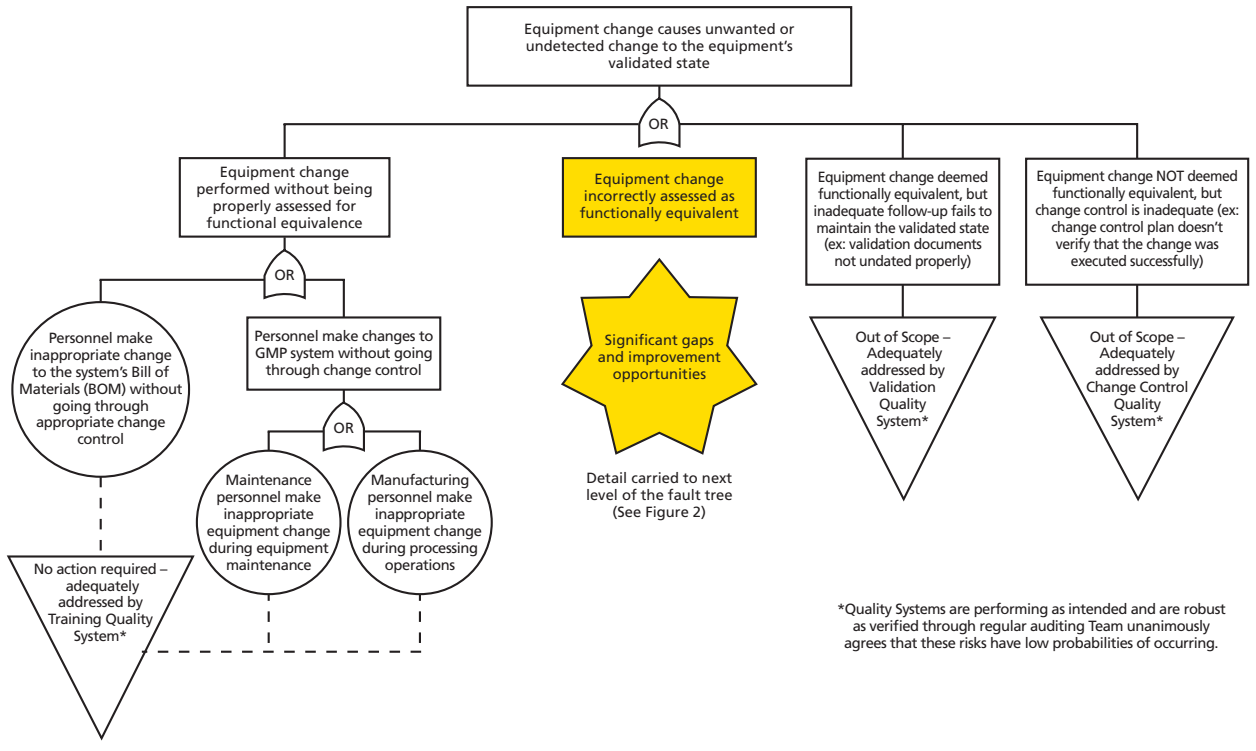
Pharmaceutical manufacturers have an obligation to ensure that their manufacturing equipment is properly designed, installed, tested, operated, and maintained throughout their service lifetimes. During these service lifetimes, manufacturing equipment will likely require both preventive and corrective maintenance activities that may involve the replacement of parts within the systems. Parts replacements must be performed under the appropriate change controls to ensure that manufacturing equipment remains in a validated state with respect to installation, operation, and performance. Change-control considerations are greatly facilitated when replacement parts are exactly identical to the original parts. However, it is not uncommon for pharmaceutical manufacturers to resort to procuring and installing replacement parts that are not identical to the original parts due to changes affected by parts suppliers (e.g., product redesigns, discontinuations). In these instances, a risk-management approach may be used to systematically assess whether replacement parts are functionally equivalent (i.e., like-for-like) with original parts to ensure proper change control while also preventing unnecessary revalidation activities.

This case study on functional equivalence for equipment replacements is the second of eight in a series put together by the Product Quality Research Institute Manufacturing Technology Committee (PQRI–MTC) risk-management working group. The series is meant to advance the understanding and application of the International Conference on Harmonization (ICH) Q9 *Quality Risk Management* guideline by providing actual examples of risk-management assessments used by the bio/pharmceutical industry. The introductory article explaining the history and structure of the series, as well as the first case study, on defining design space, appeared in the July 2011 issue of *Pharmaceutical Technology* (1).

In this case study, a risk-management approach was taken by the firm to identify the following:

- Risks associated with equipment-parts changes that

Figure 1: Fault-tree analysis (FTA) of equipment changes and associated validation impact.



might adversely impact the validated state of manufacturing equipment
- Risks associated with the process of determining whether original and replacement parts are functionally equivalent
- Proper roles and responsibilities of the functional areas involved in the process of determining whether original and replacement parts are functionally equivalent.

The outputs of the risk-management approach used by the firm included a generic, robust, and repeatable process for performing functional-equivalence assessments as well as defining organizational roles and responsibilities supporting the process.

Risk question and risk-assessment method

The risk question developed for the subject case study was: *What process and associated functional area roles and responsibilities are required in order to assess whether replacement parts are functionally equivalent with original parts in order to ensure proper manufacturing-equipment change control while also preventing unnecessary revalidation activities?*

The firm elected to craft one risk assessment for the overall (generic) functional-equivalence assessment process to achieve two objectives:
- Identify potential gaps, inconsistencies, and redundancies within the process that had historically been used for replacement-parts functional equivalence determinations
- Identify new or improved activities that would lead to robust, efficient, and consistent functional-equivalence assessments moving forward.

To support selection of a risk-assessment method, the team examined the above risk question and identified the core activities supporting the historical functional-equivalence assessment process. Core activities examined included the equipment change-control process and the maintenance-systems inventory process-control flow. The team noted the following observations:
- The functional-equivalence assessment process was historically dependent upon human judgment, expertise, and experience
- Process risks (e.g., potential breakdowns of the process) were qualitative in nature and difficult to quantify with specificity.

Given these observations, the risk-assessment team selected Fault Tree Analysis (FTA) as its risk-assessment method because it is well suited for analysis of qualitative fault conditions that may be related to human performance factors.

Risk identification, analysis, and evaluation

The risk-assessment process began with a review and analysis of the change control system to determine how equipment parts replacements could potentially cause an unwanted or undetected change to the equipment's validated state. The analysis was organized into the fault-tree structure (see Figure 1). This fault tree illustrates the po-

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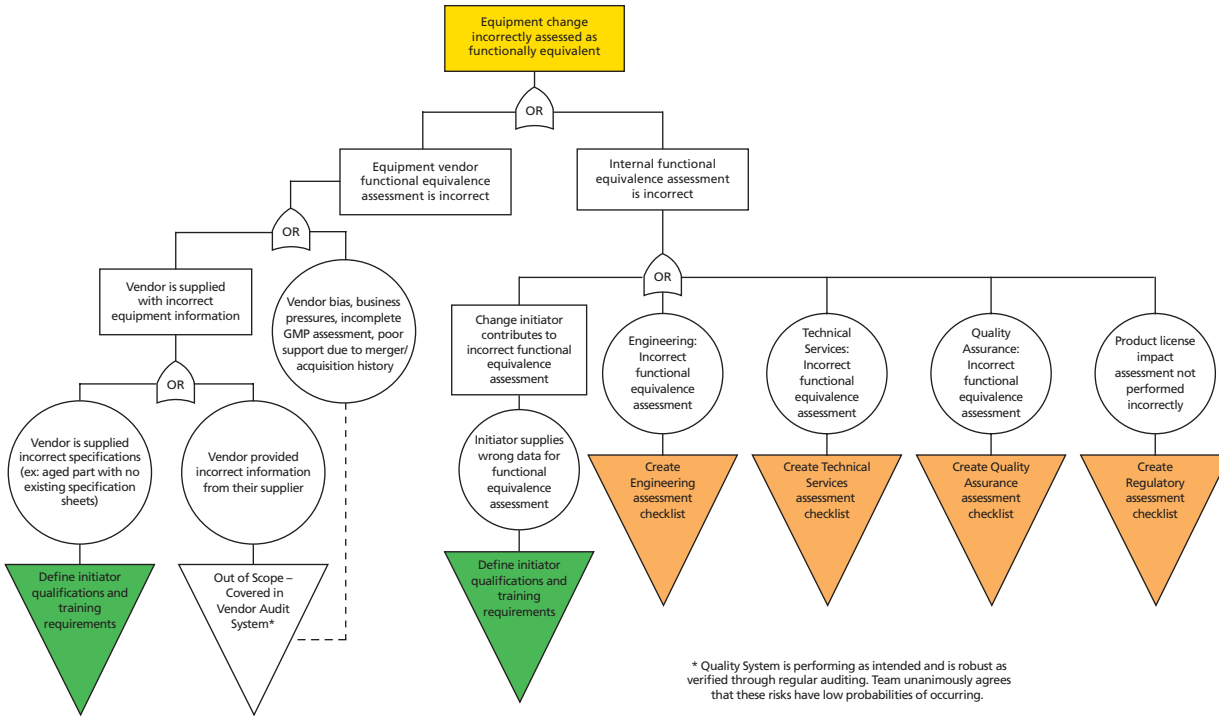
Figure 2: Fault-tree analysis (FTA) of functional equivalent assessments.



tential means by which equipment changes, such as parts replacements, could pose risk to the validated state of the equipment. The team concluded that many of the potential fault pathways were already being appropriately mitigated by robust quality systems (e.g., training, validation, and change control) that were performing as intended and that were being routinely audited. However, significant gaps and improvement opportunities were noted around the process used for the functional-equivalence assessments (see Figure 1, yellow pathway).

To further explore the risks associated with the functional-equivalence assessment process for equipment replacement parts, the risk-assessment team continued development of the fault tree as shown in Figure 2. The team focused on two key areas of risk: functional-equivalence assessments performed by parts vendors, and functional-equivalence assessments performed internally by the firm's functional areas.

The detailed FTA executed by the risk-assessment team revealed two areas of significant risk where improvement was required:

- The Initiator (i.e., petitioner and preliminary data collector) for functional-equivalence evaluations should be a subject matter expert (SME) who is appropriately trained and qualified to craft accurate initial assessments (see Figure 2, green triangles).
- Specific roles and responsibilities for each functional area participating in functional-equivalence assessments should be clearly defined (see Figure 2, beige triangles).

Risk control

For each of the two areas of significant risk identified in the FTAs and summarized above, associated risk-control plans were established, as follows:

Training curricula were created to define the training and qualification criteria for personnel initiating functional-equivalence assessments. These controls were designed to ensure that Initiators would be able to identify, compile, and/or generate the data and rationale required to support thorough and accurate functional- equivalence assessments.

Roles and responsibilities for each functional area participating in functional-equivalence assessments were delineated in the form of executable checklists designed to ensure that every functional-equivalence assessment will be performed in a thorough and reproducible fashion. Each organization identified in Figure 2 (Engineering, Technical Services, Quality Assurance, and Regulatory) created a checklist tailored to their specific roles and responsibilities that the team had collectively defined.

This approach minimized both gaps and redundancies in the assessment efforts while also providing a common assessment record format to facilitate overall review of the assessment package. Each functional area checklist details unique areas of consideration for the assessment and provides spaces for the assessment conclusions and the signatures of the assessor(s). An example checklist from the Engineering functional area is shown in Table I.

Table I: Checklist template for determining engineering functional equivalence.

Areas of consideration	Typical characteristics of functionally equivalent parts	Assessment	Performed by
Materials of construction and ratings			
• Composition of process–contact parts	Comparable materials of construction for wetted surfaces		
• Compatibility with process	Parts designed to operate at expected process extremes (e.g., heat, pressure, chemistry)		
• Surface finidhes	Comparable surface finishes that support continued effective cleaning and/or sterilization		
Inputs, outputs, capacity, and performance characteristics			
• Materials / flows	Similar mass-transfer charateristics (e.g., volume, pumping, friction loss, pressure drop)		
• Electrical	Similar electrical service requriements and electrical performance characteristics (e.g., reporting frequency, voltage)		
• Data	Data receipt and/or transmission in the same format (e.g., units, file types) and with similar performance characteristics (e.g., reporting frequency, speed)		
• Sizes	Comparable sizes (e.g., inlet size, nominal hold capacity, outlet size)		
• Metrology	Measurement tolerances, scales and units that meet process specifications and are comparable		
System connections			
• Units (for instruments, control systems)	Part connections that allow for reciept and/or transmission of data in the same format (e.g., units, file types) and with the similar performance characteristics		
• Orientation (for hardware) and configurations	Parts are physically configured (as constructed and as installed in a comparable manner so as to continue to meet process specifications and support process performance (e.g., flow, drainability, cleanability, sterilization)		
• Sizes / Locations	Parts utilize the same system connections in the facility		
Specifications (general)			
• Mechanisms of action	Parts have comparable mechanisms of action (e.g., sequence of operations, purported usage, design and operation principles)		
• Operational ranges	Parts feature comparable operational ranges across all process parameters		

Risk documentation and communication

The outputs of this risk-management effort comprise the documented justification for controlled revisions to:

- Training and qualification curricula for personnel initiating change controls where functional-equivalence will be assessed
- Equipment change control standard operating procedures that direct the functional-equivalence assessment process for parts replacements
- Maintenance-systems inventory process-control flow.

Training is required to be performed on these updated documents and training records are periodically audited for compliance.

Risk review

As part of the firm's standard practice for the ongoing maintenance of quality systems, routine audits and document reviews are performed throughout each of the quality systems impacted by this risk assessment (i.e., training, change control, and equipment maintenance). Adverse findings or trends identified during these reviews would provide indication whether the risk assessment needs to be revised.

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Developing an International Dialogue on Biologics Standards

US Pharmacopeia promotes horizontal standards and a product-class approach for quality attributes.

Tina Morris

In a study released in May 2011, US regulatory approvals for biologic drugs and biotechnology products (collectively referred to as "biologics") were reported to have nearly doubled in the past decade, compared to the 1990s. This growing market emphasizes the need for consistent approaches to product quality and public standards. In its upcoming Science & Standards Symposium on Biologics & Biotechnology, "Advancing Quality Standards through Analytics and Assays," taking place October 3-6 in Seattle, the US Pharmacopeial Convention (USP) will lead discussions on standards-setting initiatives related to biologics and the materials critical for their manufacture as a growing number of these types of drugs enter the therapeutic space.

Setting the stage for the symposium are keynote speakers Steve Kozlowski, director of the FDA Office of Biotechnology Products, and Gillian Woollett, chief scientist at the Washington, DC, law firm Engel & Novitt. Each will discuss the regulation of biologics. The following two-and-a-half days of technical sessions will include presentations from an international panel of industrial, academic, and regulatory stakeholders engaged in the development of quality standards for biologics. USP topic experts will discuss general analytical approaches and what they can do for biologics; quality attributes of biologic drugs by product class; and the US regulatory landscape for these products. An entire track of sessions will focus on bioassays and the assessment of biological potency, critical to all biological medicines.

Quality standards set by the USP—and enforceable by FDA—have traditionally been developed using what's called a "vertical approach," which is particularly suited for the characterization of small-molecule drugs. Under this approach, documentary standards (or product monographs) have been created for one drug product at a time, with associated reference materials (i.e., pure physical samples used as reference chemicals for testing) developed in tandem with monographs. General chapters in USP's official compendium, *US Pharmacopeia–National Formulary (USP–NF),* represent overarching information and testing procedures that apply across all or groups of monographs. These chapters broadly support product-specific (vertical) standards in the determination of identity, strength, and purity.

Biologics require a greater portfolio of analytical procedures than small-molecules.

Compared with their small-molecule counterparts, biologics are heterogeneous and more complex in their makeup. Thus, analysis and characterization are more challenging and require an even greater portfolio of good analytical procedures that can underpin product characterization.

Another important issue for biologics quality is the use of ancillary and process materials that are also complex biologics. Common examples are fetal bovine serum (FBS) widely used in vaccine manufacturing; cytokines like interleukin-4 (IL-4) used in the cell-therapy arena; and materials like protein A, used in monoclonal-antibody manufacturing. The quality of these materials going into the manufacturing process can have a direct impact on the quality of the medicinal product itself, especially when the end product is not highly purified and residual amounts of the ancillary material have to remain.

Working through expert committees and advisory expert panels, the USP biologics and biotechnology department has been actively revising and developing new chapters in USP–NF. Work has focused on general guidance in the form of information chapters, and also on specific test and product-class chapters that speak to the analysis of quality attributes for certain biologics product classes and the analytical procedures necessary to measure them. The goal with these "horizontal" standards is to provide more broadly applicable quality expectations in areas where analytical platform approaches already exist.

Hot topics

In deploying a horizontal approach to develop standards for biologics, USP's activities in the following areas are reflected in the themes of session tracks for the Science & Standards Symposium.

Tina Morris, PhD, is vice-president of biologics and biotechnology for the US Pharmacopeial Convention.

Bioassays. USP has developed a new suite of bioassay chapters that includes guidance and information focused on development, analysis and validation of biological assays. As a companion to these guidance chapters, USP has also developed example bioassay data sets and will make software analyses of the data available to meeting attendees. Case studies on analytical and compliance challenges related to bioassays as well as the assignment to biologics of quantities and values will be discussed.

Critical quality attributes for biologics. In the development of product-class standards, identification of critical quality attributes (CQAs) that apply across products within a designated class is key. *USP* <129> Critical Quality Attributes of Recombinant Therapeutic Monoclonal Antibodies is one example of a USP chapter in development which focuses on CQAs. In addition, *USP* <90> Fetal Bovine Serum—Quality Attributes and Functionality Tests became official in *USP–NF* in May 2011.

Ancillary materials and process enzymes. Ancillary materials, including growth factors and process enzymes, are necessary for the manufacture of certain biologics such as vaccines and cell-based or tissue-based therapies, but generally must be removed from the final product once the manufacturing process is complete. *USP* <1024> Bovine Serum addresses quality issues related to the production, sourcing, and characterization of this class of ancillary materials, with the intent of supporting its users in conducting risk assessment and implementing risk-mitigation measures.

Post-translational modifications. The functionality of a protein-based therapy is primarily based on its proper structure as well as correct post-translational modifications. *USP* General Chapter <1084> Glycoprotein and Glycan Analysis—General Considerations has been developed to address modifications that result from the process of glycosylation. In addition, USP currently is working on two chapters addressing compendial procedures for oligosaccharide and monosaccharide analysis, important for the manufacture of glycosylated proteins.

Analysis and regulation of bioassays. As technological improvements emerge, capabilities regarding bioassays must be updated to parallel those changes. Transitioning legacy products away from animal-based potency assays is an important issue for manufacturers. USP guidance chapters include <111> Design and Analysis of Biological Assays, which provides direction to users on developing appropriate strategies regarding biologic potency.

The topics of the conference speak broadly to industry professionals engaged in the development, analysis and quality control of biological medicines, as well as to professionals interested in the regulatory and compendial issues related to the latest trends in biotechnology. In support of its nearly 200-year-old mission to advance public health, USP is committed to continuing this global dialog among manufacturers, regulators, and practitioners to address the need for public quality standards for biologic medicines. **PT**

For more information on the symposium, visit: www.usp.org/meetings/asMeetingIntl/seattleEvent.html.

Offshoring Biomanufacturing

Eric Langer

China rises to the top as a destination for international outsourcing.

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PharmTech.com/outsource

Trends in Asia biomanufacturing stood out this year in BioPlan Associates' *8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (1). The study asked respondents to consider their five-year time horizon to 2015 and evaluate their facility's current plans for international (i.e., nondomestic) capacity expansion. For the first time, China ranked highest in the world with 17% of respondents identifying the country as a potential biomanufacturing outsourcing destination. India was the choice of 13.2% of respondents, and Singapore was selected by 9.5% of respondents. The United States was chosen by 15.1% of respondents (see Figure 1). The results show that the demand for biomanufacturing capacity in Asia in serving regional or domestic markets can outweigh managerial concerns when offshoring manufacturing. This year's survey had responses from 352 global biomanufacturers and covered issues associated with production bottlenecks, budget trends, use of disposables, downstream production, and quality management (1).

These findings support the continuing rise of Asia as a global biomanufacturing power. In coming years, many biopharmaceuticals originally launched in Western markets in the 1980s and 1990s, including many blockbusters, will be coming off patent. Multiple biosimilar and bio-better versions are likely to be marketed for each product, thereby resulting in a significant expansion of companies developing and manufacturing biopharmaceuticals. Although the great majority of biopharmaceutical manufacturing and consumption in emerging markets currently involves biogenerics or other copies of products developed by Western innovator companies, these foreign markets, although still relatively small, are growing at a more rapid pace than major Western markets.

Inside the numbers

According to BioPlan's recently released *Top 1000 Global Biopharmaceutical Manufacturing Index,* China holds 8.5% of the global concentration of capacity and employment, India 8.0%, and Japan and other Asian countries 9.2%; these areas are growing more rapidly in biomanufacturing capacity than the global average. Asia-Pacific has one of the largest concentration of global biopharmaceutical manufacturing capacity (2). Asia's combined share of 25.7% of global concentration of capacity and employment virtually matches Europe's share at 26.2% and is gaining on North America's share of 37.5%. These results show that the biopharmaceutical industry is becoming increasingly international in scope and is beginning to move away from its exclusively US and European focus as larger manufacturers locate in emerging markets to support regional markets and provide backup manufacturing for products in major markets. The BioPlan study suggests that biopharmaceutical research and development, both for biosimilars and innovative products, is increasing in China, India, Russia, and select emerging markets (2).

Also, many large Chinese and Indian companies are developing commercial-scale biopharmaceutical manufacturing facilities to serve domestic and regional needs. This trend is evident in vaccine manufacturing. An important development occurred earlier this year in March, when the World Health Organization (WHO) reported that China's State Food and Drug Administration was shown to comply with international standards for vaccine regulation. With a regulatory system for vaccines documented to comply with international standards, vaccine manufacturers in China are now eligible to apply for WHO prequalification of specific products. Prequalification, which is a guarantee that a specific vaccine meets international standards of quality, safety, and efficacy, is a prerequisite for manufacturers to supply to countries through UN procuring agencies (3).

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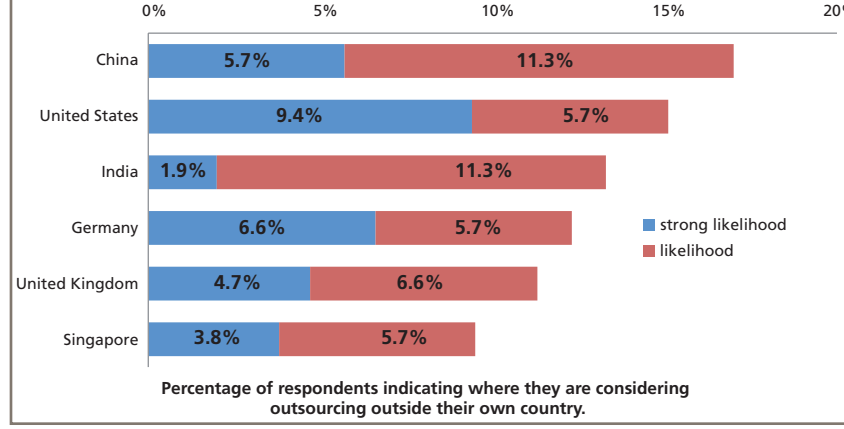
Figure 1: Destination for international outsourcing of biomanufacturing.



Percentage of respondents indicating where they are considering outsourcing outside their own country.

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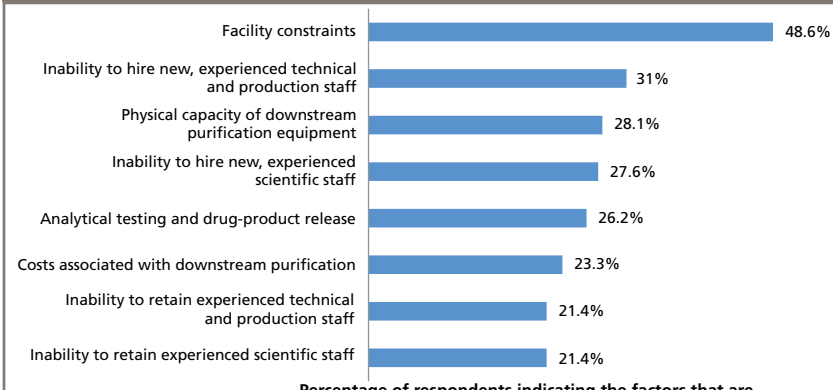
Other effects

Along with biopharmaceutical manufacturing growth in Asia comes opportunity for vendors, such as providers of equipment and consumables. The BioPlan study shows that more than half of respondents specifically sell to India and China, and 38.7% of all vendors sell in other Asian markets (2).

The growth of emerging countries also contribute to a tightening of the global scientific labor markets. This year's survey showed that concerns over hiring are increasing as the global economic downturn stabilizes. Expectations of constraints due to the "inability to hire new, experienced scientific staff" jumped from 19.1% of respondents in 2010 to 27.6% in 2011. The survey, which compiled the factors likely to create biopharmaceutical production constraints by 2015, found that facility constraints (48.6%) topped the list, followed by the "inability to hire new, experienced technical and production staff" (31%) and the "physical capacity of downstream purification equipment" (28.1%) (see Figure 2). This tightening for experienced bioprocessing specialists may be due to expansions in growth of operations and further exacerbated by specialists increasingly spread out over a growing number of biopharmaceutical companies worldwide.

Figure 2: Select factors creating future capacity constraints.



Percentage of respondents indicating the factors that are likely to create biopharmaceutical production capacity constraints at their companies' facilities by 2015.

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2. BioPlan Associates, *Top 1000 Global Biopharmaceutical Facilities Index*, www.top1000bio.com/index.asp, accessed June 20, 2011.
3. WHO, "China's State Food and Drug Administration Gets WHO Approval for Vaccine Regulatory System" Press Release, Mar. 1, 2011. **PT**

Catalent Gives Talk at Solubility Summit

Julien Meissonnier, director of research and development for Catalent Pharma Solutions, gave a presentation titled "Enhancing the Bioavailability of Poorly Water-Soluble Drugs: Oral Lipid-Based Formulations" at the Seventh Annual Improving Solubility Summit in London on June 28–30, 2011. Meissonnier and René Holm, head of preformulation at Lundbeck, spoke about commercially proven drug-delivery solutions that improve the solubility and bioavailability of new chemical entities.

Meissonnier highlighted emerging solutions, such as softgel technologies, that overcome obstacles related to stability and absorption and improve performance. He also shared expert considerations and perspectives about the future of oral lipid-based formulations. The conference included discussions of the latest techniques and technologies for poorly water soluble drug candidates.

Evonik Degussa Purchases Twin-Screw Extruder

Evonik Degussa purchased a Leistritz Nano 16-mm twin-screw extruder (TSE) to serve the growing number of customers using pharmaceutical melt-extrusion technology. Installed at the Evonik Pharma Polymers Technical Laboratory in Piscataway, New Jersey, the new extruder is equipped with a microplunger feeding system and precision T-12 K-Tron top feeder. The company will use the TSE to mitigate the solubility and bioavailability problems of poorly soluble drug substances, to achieve taste masking, to provide controlled or sustained release, and to perform continuous manufacturing applications.

TSEs often are used to manufacture pharmaceutical products from feasibility to commercial scale. "At early stages of melt-extrusion formulation development of new molecular entities with limited drug availability, it is essential to use extrusion equipment for the smallest batch size," said Firouz Asgarzadeh, senior technical manager of Evonik's Pharma Polymers business line, in a press release.

Smithers Names New President

Smithers Pharma Services promoted Prasad Raje to the position of president of Smithers Pharma Services. Raje will report to Michael Hochschwender, president and chief executive officer of Smithers Group.

Raje joined the Smithers organization in October 2009 and has served as executive vice-president of Smithers Viscient since February of 2011. In addition to his duties with Smithers Viscient, he had operational responsibility for Smithers Pharma Services. Raje's background includes expertise in drug discovery and organic process research and development leading to the commercialization of active pharmaceutical ingredients. He also has experience conducting due diligence, acquisitions, and integrating businesses.

Smithers Pharma Services provides formulation services, analytical chemistry, preclinical and clinical bioanalytical testing, and extractables and leachables testing. The company also performs in-house storage stability studies.

Q&A with

Terry Novak, *president of Norwich Pharmaceuticals*

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

Novak:
The contract manufacturing organization (CMO) industry faces a reputation issue. People think we're mediocre. There's still a stigma, a perception that Big Pharma can do drug manufacturing better than outsourcing providers. While that perception has slightly changed during the past five years, proving the case for CMO partnership remains our most time-intensive challenge. CMOs have to be as good as the customer's own manufacturing, which means delivering finished product on time, and right the first time. The greatest strength the CMO industry now has is its strong regulatory compliance. Where CMOs need to do a better job is on-time delivery. For specialty and small pharmaceutical companies, we are their internal supply, and we always have to remember that. I think a lot of CMOs have lost their customer focus due to the financial issues that have affected their businesses during the past few years.

PharmTech:
Do you see a new industry trend emerging?

Novak:
Drug delivery is still a hot topic. We see many companies trying to extend the patent life of an existing product before it loses exclusivity. Specifically, nanotechnology has been talked about forever, but no one has put it to commercial use yet.

Everyone is still talking about ePedigree. We were preparing for the California legislation about two years ago to force this issue into becoming a trend, and although it didn't happen, I believe it's inevitable. On the packaging end, this will be a big emerging area that we're going to have to address.

PharmTech:
What is the most common demand your clients are currently making of you?

Novak:
Lately it's been formulation development for products that are poorly soluble. They're difficult to manufacture, and outsourcing providers should be looking to solve that problem. It's an area that we've expanded into, whether it's highly potent compounds or complex controlled-release delivery. During the next few years, growth in the contract manufacturing business will be achieved by companies that can provide a quality solution to complex formulations.

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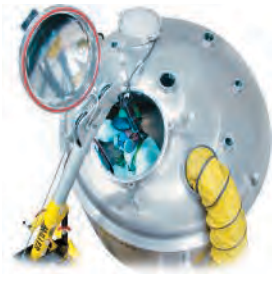

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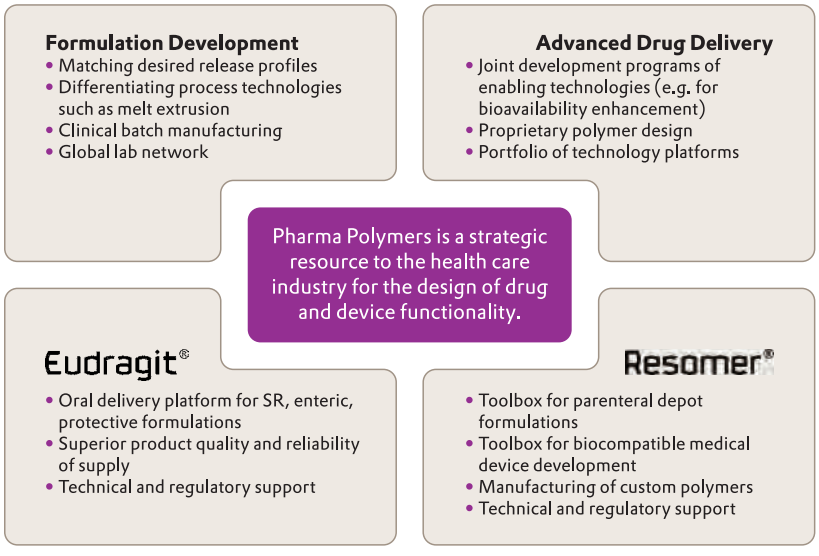

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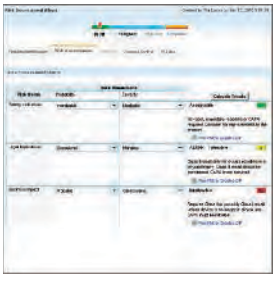

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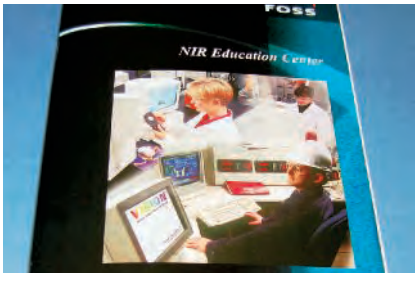
- Optimized probes for reflectance, transmission or transflectance
- Single point or multiplexed (up to 9 sampling points per instrument)
- Standard NEMA 4X/IP65 rated. Can be upgraded to meet most electrical classifications (C1D1, C1DII, ATEX, etc.)



FOSS NIR Education Center

The FOSS NIR Education Center was established in 2006 to promote knowledge and understanding of Near Infrared technology. The Center offers a variety of courses covering FOSS NIR instrumentation, Vision software, general and specific customer NIR applications, and validation of near infrared methods to address the requirements of regulatory agencies. Order your free Course Catalog today!

New Articles from FOSS NIRSystems

Order your free reprints of our newest NIR articles:

- Near-Infrared (NIR) Analysis of Tablets Containing Two Active Ingredients
- Extending Calibrations for NIR Assay of Tablets Using Synthetic Modeling and Variance from Placebos
- Monitoring Viable Cell Density in Bioreactors Using NIR Spectroscopy Real-Time
- Bioreactor Monitoring of Osmolality and pH Using NIR Spectroscopy

The XDS MasterLab – your complete NIR System

- Automated transmission or reflectance analysis of a tray of multiple tablets, capsules, or vials
- Non-destructive analysis of solids and liquids in less than a minute
- No sample preparation, no reagents, no waste
- Network-ready analyzer for centralized database management

GEMÜ Valves

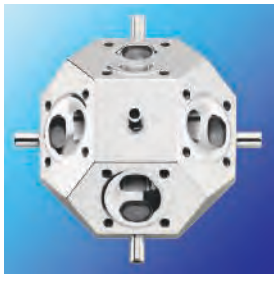
3800 Camp Creek Parkway
Bldg. 2600, Suite 120
Atlanta, Georgia 30331
tel. 678.553.3400, fax 678.553.3459
www.gemu.com

The Gemu 651 unitized valve / actuator / pilot valve / position indicator, offers a unique solution in confined areas, particularly for fractional sized valves and small multiport configurations. The control top segment is interchangeable with a 4-20 electro-pneumatic positioner module.

The Gemu 1236 Position Indicator features highly visible luminous indication, self setting switch points and local or remote programming. Continuous analogue sensing with microprocessor controlled setting offers enhanced repeatability and reliability. Optional AS-I interface or IO-LINK enabled communication.

The Gemu 1434 Electro-pneumatic Valve Positioner is smart but not superfluous. It offers a plug and play, auto-initializing positioner for linear valves up to 25 mm stroke in a stainless steel economical NEMA 4X enclosure. Remote mounting is optional.

The Gemu 4222 Valve Communication Module innovative continuous sensing technology plus self setting switch points offer unprecedented repeatability and reliability. Rotary or linear sensing and an integrated 3/2 pilot valve are contained in a common stainless steel enclosure. Remote programming is available via AS-I, DeviceNet or discrete 24 VDC signals.



M600 Multiport Sanitary Block Valves provide solutions to piping challenges, retained volume limits, drainability issues and space constraints while providing enhanced efficiency and simplified validation. A broad range of porting configurations facilitates modeling in complex piping systems.

The Gemu 688 Sanitary Diaphragm Valve provides two-stage flow with an intermediate setting that is mechanically adjustable from 0 – 100%. Fast and precise filling rates with reduced foaming or frothing are attained in a single valve for dribble control without a costly modulating control system.

Hospira One 2 One®

275 North Field Dr.
Lake Forest, IL 60045
tel. 224.212.2267
tel. +44 (0) 1926 835 554
one2one@hospira.com
www.one2onecmo.com

ONE 2 ONE®
A Service of Hospira

Hospira's One 2 One® business is a world leader in the custom development and manufacture of injectable products packaged in vials, prefilled syringes, cartridges, and flexible containers. Hospira has over 80 years of know-how in parenteral drug commercialization, and One 2 One has over 20 years of contract manufacturing experience serving the bio/pharmaceutical companies.

Our Comfort Zone is Here:

By centralizing management, One 2 One can thoroughly integrate nine state-of-the-art manufacturing facilities around the world. Our global network of facilities offers a wide range of development, drug delivery, and manufacturing capabilities and services. One 2 One has a wealth of history and experience in global injectable product commercialization.

Broad Sterile Manufacturing Experience

- Sterile filling and lyophilization in the U.S., Italy, Australia and India.
- Manufactured over 25 different monoclonal antibodies, proteins, peptides and recombinant vaccines.
- Extensive experience manufacturing emulsions, cytotoxic products and beta-lactam products.
- Practical knowledge of 70 markets, including expert regulatory filing strategies for the Americas, Europe, Asia Pacific regions.

Drug Delivery Systems

One 2 One provides a wide variety of delivery options, from vials, bottles, and prefilled syringes, to proprietary products such as the VisIV™ flexible container. It's about developing simple solutions to streamline administration, improve accuracy, and decrease waste and costs. One 2 One meets your unique product needs for a distinct advantage in the marketplace.

iSecure™ Prefilled Syringe

As a prefilled, unit-dose disposable injection syringe, iSecure™ delivers efficiency and simplicity to ensure accuracy and lower costs. iSecure™ utilizes a 1 to 2.5 mL cartridge and is designed for compatibility with intravenous administration sets and has the flexibility to be used for intramuscular injections.

Onco-Tain™ Vial

Our proprietary Onco-Tain™ vial packaging option was designed to contain cytotoxic material by providing shatter resistance with a PVC bottom, surface protection with a shrink-wrapped sleeve and clarity of glass for easy inspection. We highly recommend this vial packaging option for your cytotoxic products.

I Holland Americas

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Fort Myers, FL 33905
tel. 732.310.4433, fax 239.214.0259
ihollandtools@comcast.net
www.iholland.co.uk

Specialist Tooling Manufacturer

Because I Holland only manufactures tablet compression punches and dies there are no other distractions. We focus all our experience on precision engineering the best tool for the tablet that is being produced. We don't sell tools from stock, every punch and die we manufacture is crafted to meet the specific requirements of the product that you are producing.

New U.S.A. Showroom & Training Facility

I Holland Americas new Sales & Technical Support Center located in Fort Myers, Florida opens in September 2011. This Center will be providing training and around the clock support to I Holland customers located throughout the Americas as well as demonstrating and providing trial facilities for our wide range of PharmaCare™ equipment.

PharmaGrade Steel

Selecting the right steel is key to the successful performance of tablet compression tooling. This will achieve an optimum balance and at I Holland we have achieved exactly that with our quality PharmaGrade range through which we are able to offer an optimum steel for all punch and die applications - offering ESR at no extra cost to you.

PharmaCote Solutions

I Holland's PharmaCote range is a suite of treatments and coatings that enhance the performance of substrate material for punches and dies. Our PharmaCote range is focused on:

- Improving anti-stick properties
- Improving surface hardness
- Improving wear resistance
- Improving corrosion resistance

PharmaCare™ 7-Step Process

It's simply good business sense to maintain and store your punches and dies correctly and you will produce a better product for longer, reduce costs and enhance profitability. The PharmaCare™ 7-Step Process is a planned maintenance and storage programme which will contribute more than it costs to your company's turnover.

Holland Automated Cleaning System

As the first part of the 7 Step Process the Holland Automated Cleaning System or HACS has been designed to clean high volumes of tooling quickly and efficiently with minimal handling by operators therefore reducing the risk of cross contamination and corrosion.

International Centre for Diffraction Data

12 Campus Blvd.
Newtown Square, PA 19073
tel. 610.325.9814
fax 610.325.9823
www.icdd.com

PDF-4/Organics

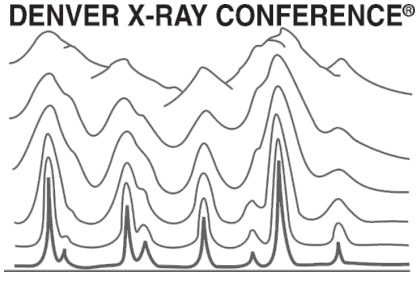
Our materials identification database provides comprehensive coverage as the world's largest X-ray powder diffraction database for organics and organometallics. PDF-4/Organics is designed for a multitude of applications in pharmaceutical, regulatory, specialty chemical, biomaterials and forensic fields. PDF-4/Organics is produced by combining drug active compounds with polymers (including starches and celluloses), common inorganic salts, excipients and pharmaceuticals.

PDF-4+

PDF-4+ is an advanced database with comprehensive material coverage for inorganic materials. It contains numerous features such as digitized patterns, molecular graphics and atomic parameters. Many new features have been incorporated into PDF-4+ to enhance the ability to do quantitative analysis by any of three methods: Rietveld Analysis, Reference Intensity Ratio (RIR) method or Total Pattern Analysis.

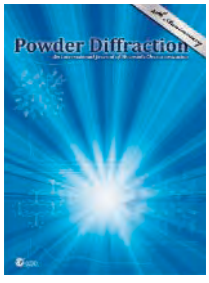
Pharmaceutical Powder X-ray Diffraction Symposium

This annual symposium is designed to create a forum for the exchange of knowledge and cutting-edge ideas among those interested in the combined fields of XRD and pharmaceutical sciences. PPXRD presents topics on patent and regulatory issues, formulation, product development, drug delivery, polymorphs, amorphous and nanomaterials, and complimentary techniques.



Denver X-ray Conference

DXC is the world's largest annual conference dedicated to the fields of X-ray analysis. Experts in the field of X-ray diffraction and X-ray fluorescence gather for a week of workshops, technical sessions and manufacturers' exhibits. For information on the conference please visit www.dxcicdd.com.



Powder Diffraction Journal

ICDD's quarterly international journal focuses on materials characterization employing X-ray powder diffraction and related techniques. With feature articles covering a wide range of applications, from crystal-structure determination of polycrystalline materials to advances in application software and hardware, this journal offers a wide range of practical applications.

ICDD Clinics

ICDD offers a variety of educational products designated to teach and instruct both the new and experienced user. ICDD Clinics are taught by experienced instructors that have a variety of scientific backgrounds. This diversity enables the attendees to receive a blend of both theory and results-oriented practical experience.

Jost Chemical Co.

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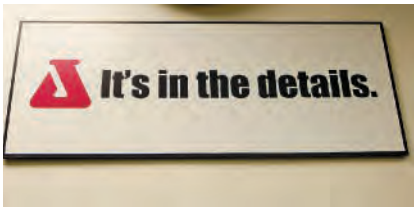
www.jostchemical.com



Company Overview

For 26 years Jost Chemical Co. has manufactured high purity specialty chemicals for the pharmaceutical, nutritional, food and reagent markets. Jost's St. Louis, MO site is comprised of two manufacturing buildings and 150 employees of which over 25% have technical degrees. From the beginning, Jost has focused on product quality through controlled validated processes and lot-to-lot product consistency.

cGMP

Jost's 190,000 ft^2 /17,000 m^2 manufacturing site is FDA registered and operates under ICH Q7 bulk pharmaceutical cGMP. Our high purity chemical salts are manufactured to meet USP/EP/BP/JP/ACS and multi-compendial requirements and are BSE/TSE free.

Traceability

Jost adherence to GMP manufacturing assures that all finished products are fully traceable "backwards" to the raw materials and "forwards" into the final packaging and ship-to location for every container comprising the production lot.

Quality Documentation and Support

Jost understands you need immediate and accurate responses to inquires for technical information. Our experienced and dedicated technical staff responds quickly and thoroughly to your requests for product solutions, information, and specific test requirements.

Custom Manufacturing/ Packaging

Jost will meet your specific product requirements and develop a DMF, ASMF and CEP if required. Packaging options include fiber drums, poly drums, poly pails, cartons, super sacks, etc. Custom packaging is available.

In-House Testing

Jost manufactures 250+ products and all are fully tested in house. With our on-site instrument and wet chemistry capabilities, we can successfully address demanding applications from initial concept to finished products.

Lancaster Laboratories, Inc.

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PO Box 12425
Lancaster, PA 17605-2425
tel. 717.656.2300, fax 717.656.3772
www.lancasterlabspharm.com

Celebrating 50 Years

Biopharmaceutical Services

Lancaster Laboratories provides a broad range of laboratory services supporting the biopharmaceutical industry. These services include cell and molecular biology (cell-based assays, ELISA assays, nucleic-acid analysis, PCR, cell-line testing), virology (viral safety and viral clearance), biochemistry (biochromatography, electrophoresis, mass spectrometry, protein quantitation and characterization), and support for facility and process validation.

Method Development/Validation

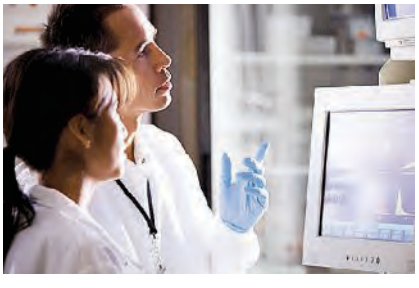
Our staff of scientists offers extensive method development and validation services. Methods for stability and release testing, as well as, process and cleaning validation, in support of large and small molecules drug products, drug substances, comparator products, excipients and raw materials are offered. Method qualification/validation can be conducted using protocols developed by Lancaster Laboratories or the client.

Stability Services

We specialize in supporting stability studies, with services ranging from protocol writing to storage and testing through tracking and trending of data. The company is experienced in testing solid-dosage forms, liquids, suspensions, transdermals, aerosols, and comparator products. Stability storage consists of 26 different temperature and humidity conditions with more than 22,000 ft^3 of storage space.

Raw Materials Services

Lancaster Laboratories provides extensive capabilities in Raw Materials testing. Testing is conducted using compendia (USP, EP, JP, BP, FCC, ACS) and client/vendor supplied methodology. A multiple shift operation with extensive laboratory capacity provides exemplary service and meets delivery needs. Expedited and customized programs are also available upon request.



Innovative Scientific Staffing Solutions

Our innovative Professional Scientific Staffing services solve pharmaceutical and biopharmaceutical clients' co-employment challenges. Professional Scientific Staffing provides our full-time scientists at the client's facilities; while Full Time Equivalent offers dedicated analysts for clients' projects at our facility. Award winning HR best practices, IRS 20-Factor indemnified and 50-year outstanding laboratory services reputation available at your site or ours.

Microbiology

In a 9000-ft^2 suite of laboratories designed for efficiency and contamination control, Lancaster Laboratories performs a full array of microbiological testing in support of sterile and nonsterile products and environmental monitoring and control. Services include sterility testing using isolator-barrier technology, mycoplasma testing, endotoxin and preservative-effectiveness testing, microbial limits testing and organism identification, and laboratory support for facility validation.

Lonza AG

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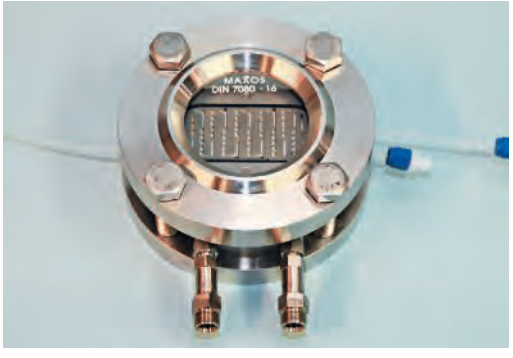
tel. +41 61 316 81 11, fax +41 61 316 91 11
contact@lonza.com
www.lonza.com



Lonza

Lonza Microreactors & Continuous Flow Services

Lonza Continuous Flow Microreactors. Our latest microreactor technology is designed to ensure complete scalability from small flow rates to large throughput, enabling consistent scale-up from a few grams to several tons of product.

Microreactor technology is based on continuous plug flow reactors. Lonza has designed micro-reactors that allow processes to be developed in the lab and easily transferred to the production environment. Batch processes have been replaced by continuous operating modules that provide automated process control and reduce operating expenses.

Microreactor technology is a new technology to the field of chemical engineering and organic synthesis that embodies the principles of Green Chemistry. Lonza's continous flow microreactor technology is designed to ensure complete scalability from small flow rates to large throughput, enabling consistent scale-up from a few grams to several tons of product.

Lonza MicroReactors Product Features:

- Compact, modular, robust (over 100 bar)
- Hastelloy for chemical resistance, aluminum for heat exchange
- Consistent scale-up from laboratory to large-scale manufacturing totally avoiding parallelization / numbering-up strategies
- Has been tested for several Lonza products up to ton scale

Lonza Continuous Flow Services Offer:

- More than 100 year experiences on flow processes
- Highly flexible and versatile flow laboratories
- In-house proven and multi-purpose flow manufacturing capabilities
- Know-how & solutions with key flow issues including plugging and long term stability

For further detailed information about Lonza's MicroReactors or other products and services, visit us at www.lonza.com, or contact us at microreactor@lonza.com.

Meissner Filtration Products

4181 Calle Tesoro
Camarillo, CA 93012
tel. 800.391.9458
+1.805.388.9911 (International)
www.meissner.com

TepoFlex® & FluoroFlex® Biocontainers

Meissner drives innovation with industry firsts - TepoFlex® - the industry's first PE based biocontainer without slip agents - and FluoroFlex® - the industry's first multilayer PVDF biocontainer. TepoFlex® 2D & 3D biocontainer assemblies are available in standard configurations (50 mL – 1,000 L). FluoroFlex® is available in standard 2D configurations (50 mL – 20 L).

UltraCap® H.D. Filter Capsules

High Capacity UltraCap® capsules provide single-use convenience for critical filtration applications requiring high-flow/throughput. UltraCap® H.D. is available in T-style and Inline versions, and can be selected in lengths of 10", 20", 30", 40" and 50". Robust in design, the UltraCap® H.D. performs well in demanding environments.

One-Touch® Single-Use Systems

Meissner's One-Touch® single-use systems portfolio delivers optimized fluid handling to the biopharmaceutical industry. Designed to offer unprecedented fluid integrity performance, TepoFlex® biocontainers deployed in either FlexStation® rigid outer containers or drums provide integral fluid management for shipping and storage needs. Visit www.meissner.com/products/onetouch.shtml for more information.

Membrane Filters

Membrane filters (0.04 µm - 1.0 µm absolute) are available in SteriLUX® and Steridyne® PVDF, EverLUX® and STyLUX® PES, Chemdyne® PP, and Ultradyne® PTFE. Configurations range from syringe and disc filters, to capsules and high capacity capsules and cartridge filters. (Microfiber prefilters to 99 µm are also available in PP, glass fiber and depth media).

BioFlex™ Tubing Sets

BioFlex™ tubing sets are designed for secure fluid transfer in critical biopharmaceutical processing applications. These single-use tubing and filter/tubing assemblies offer maximum convenience and flexibility in single-use systems. They can also be used in conventional or hybrid facilities to connect single-use and stainless steel processing equipment.

www.meissner.com

Visit our site to Download our newest biocontainer Standards Guides today! Our One-Touch® single-use Standards Guides feature TepoFlex® and FluoroFlex® assembly configurations designed to accommodate common fluid handling applications with lead times of only 3-4 weeks, and can be used to streamline the design of custom biocontainer assemblies.

Metrics, Inc.

1240 Sugg Pkwy.
Greenville, NC 27834
tel. 252.752.3800
marketing@metricsinc.com
www.MetricsInc.com

Company Overview

Metrics Inc., a fast-growing CDMO, occupies a 92,000-ft² state-of-the-art analytical testing, pharmaceutical development and manufacturing facility. Our veteran formulation development staff averages more than 17 years' career experience in pharmaceutical development and is supported by a team of 120+ analytical chemists. Services include oral dose formulation development, analytical method development and validation, microbiological testing, stability storage and testing, raw material release, trace element testing, and routine analysis of dosage forms.

CTM Phase I, II, III

Metrics' expanded CTM capabilities offer greater capacity with all clinical trial phases. Our new flexible manufacturing facility and equipment can handle up to 450-kilo batch sizes. Metrics also offers expertise in over-encapsulation for comparator studies, as well as potent drug handling capabilities. CTM packaging and labeling is also available.

Commercial Manufacturing

Seven large-scale manufacturing and packaging rooms for Phase III clinical trial and commercial manufacturing ensure high-quality manufacturing of solid oral dose formulations, including DEA II-V controlled products. Full analytical support is available – release testing, stability, microbiology testing, and custom analytical development and validation.

Fast-Track First-Time-In-Man Studies

Metrics has successfully delivered material for more than 120 critical FTIM studies. Our process ensures speed and accuracy, with a 16-24 week timeline from receipt of well-characterized NCE to shipment. Services include handling of potent products, stability studies, analytical methods development and validation. Choose blended powder in capsule or pure API in a labeled bottle.

Potent Products

Metrics' segregated potent facility provides total engineered containment through customized, hard-wall isolation technologies. Containment is achieved at 30 nanograms pcm of room air; equipment and change parts are dedicated exclusively to potent use. The facility features independent entry, exit and equipment double airlocks, decontamination showers, dedicated washroom, dedicated equipment storage and pass thru for product/waste.

Pharmaceutical Formulation Development

Services include: Tableting, instant release, controlled/matrix release, bi-layer, sustained release, capsule filling, over-encapsulation, milling, micronizing, enteric coating, ointments, creams and liquids. Metrics' processes included handling of potent products. Metrics' SOPs are geared toward all phases of the FDA submission process.

METTLER TOLEDO

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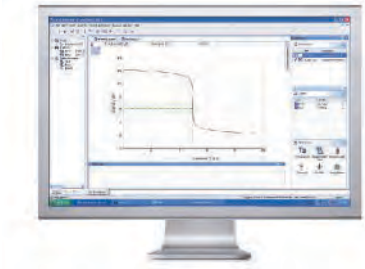
GTP™

Good Titration Practice™



Safeguard Your Work and Visualize your Results

DSC instrumentation coupled with video microscopy.

Let's face it, thermal characterization of pharmaceutical substances can be a challenging endeavor. Residual moisture, solvent and additives can add to the complexity of understanding your DSC measurement curves. Our video microscopy add-on provides visual information so you can watch how your material behaves throughout the course of the measurement.

- Correlate sample video images and DSC data
- Easy plug and play capability
- Enhances interpretation of complex curves

Good Titration Practice™ covers the entire lifecycle of a titration system. Reliable titration starts long before daily routines: A requirements-based selection of the system, as well as professional installation and training form the basis for dependable and risk-free titration. Check your titration risk in a 5-minute online assessment at www.mt.com/gtp-riskchecker.

LabX™ Titration is a powerful yet easy-to-use software platform designed to manage titration analyses and resulting data. LabX pro facilitates compliance to 21 *CFR* Part 11 with features such as audit trails, user/account management and electronic signatures. Meeting the needs of the smallest company through to the largest global enterprise, LabX™ incorporates a wide range of features that will enhance the efficiency of workflows in the QC lab. Learn more at www.mt.com/labxtitration.

MPI Research

54943 North Main St.
Mattawan, MI 49071
tel. 269.668.3336
fax 269.668.4151
www.mpiresearch.com

Reference Standard Management

Comprehensive on-site analytical services define and maintain exacting standards from purity and chemical structure through storage and stability. Reference materials are characterized according to EPA and FDA GLP guidelines, following in-house standard operating procedures and/or the methods you provide. API, reference standards, and formulated drug product characterizations following cGMP guidelines are also available.

Environmental and Food Safety Testing

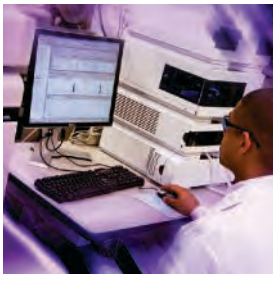
MPI Research leads the industry in fluorochemistry analysis, with over a decade of experience across a wide array of matrices. We use state-of-the-art equipment, have ample capacity, provide customized sample collection kits, and have low reporting limits. In the environmental arena, we have developed a definitive test method for bisphenol A (BPA).

Dose Formulation Analysis & Method Development

Our collaborative team works with you to develop and validate methodologies for small and large molecules in a variety of biomatrices, supporting all phases of the drug discovery and development process. MPI Research has extensive experience with GLP/cGMP-compliant dose formulation analyses including stability, homogeneity and potency for solutions, suspensions, oils, and diet vehicles.

Immunology

MPI Research provides a comprehensive—and rapidly growing—suite of immunology services executing both GLP and non-GLP studies. With expertise in areas associated with autoimmunity, immunomodulation, infectious disease, and vaccine technologies, our experienced staff offers a broad base of in-depth knowledge to support the preclinical development and evaluation of innovative therapies.



Bioanalytical Analysis for Small Molecules, Peptides and Proteins

Senior scientists develop and validate assays to support development from preclinical to Phase I through IV clinical research. Our specialized capabilities include mass spectrometry of small molecules, proteins, peptides, thermal analysis, immunochemistry, and residue analysis (including independent laboratory validations (ILV) for crop protection and method trials for animal health).

Antibiotic Potency Testing

The experienced microbiology staff at MPI Research performs antibiotic potency testing using well-established reference standards and industry-leading instrumentation to ensure antibacterial activity throughout the dated life of products from contact lens solutions to animal feed.

Natoli Engineering Company, Inc.

28 Research Park Circle
St. Charles, MO 63304
tel. 636.926.8900
fax 636.926.8910
www.natoli.com

Tablet Compression Tooling

For over 35 years, Natoli has manufactured punches and dies of unparalleled quality. Maintaining highly efficient and organized manufacturing facilities with a one-year inventory of steel ensures consistent, quality product regardless of industry demand and availability. All Natoli tooling is available for worldwide delivery.

Die Segments

Natoli is proud to be the only licensed manufacturer of Fette die table segments. Through an advanced system of micro-precision engineering, Natoli manufactures standard round, special shape, multi-tip and carbide lined die segments of exceptional quality. All Natoli segments are delivered quickly, worldwide, at competitive prices.

Tablet Presses

Natoli offers a diverse line of tablet presses to meet specific tableting needs. The new NP-RD10A single-station laboratory press is ideal for R&D when only small samples are available. The NP-500 series is a double-sided, rotary press designed to compress tablets requiring extra deep fill and extended dwell time.

Tablet Press Replacement Parts and Turrets

Natoli stocks over 300,000 quality replacement parts for nearly every tablet press on the market, making it possible to provide quality parts at incredible prices – faster than anyone else in the industry. Natoli also offer custom-built turrets and will repair turrets of any size and specification.

TM-II LVS

Natoli's TM-II LVS is the most efficient inspection system available to manage your entire tool database. Designed to help tablet manufacturers improve tablet quality and consistency by organizing critical punch inspection dimensions through a user-friendly, comprehensive tooling database. The LVS device features modern dual laser technology to ensure accurate inspections.

Accessories Catalog

The completely redesigned Tablet Compression Accessories Catalog is the most comprehensive collection in the industry. Offering over 1,500 products available for shipment worldwide, the 184-page, full-color catalog is a complete accessory guide for tablet compression. A new interactive digital version is now available online!

Optima Group pharma

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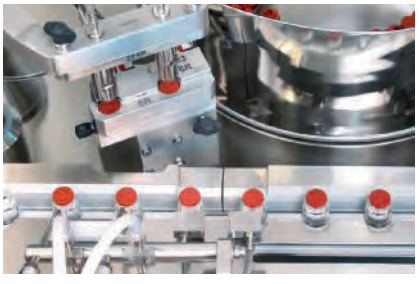
www.optima-pharma.com

Our headquarters are located in Schwaebisch Hall, Germany. Leading filling and packaging expertise for liquid and powdery pharmaceuticals and diagnostics, perfect closure systems and the complementary upstream and downstream equipment is integrated into flexible lines. The complete product range is enhanced by freeze drying systems, including loading and unloading for complex turnkey applications.

Clean room technology provides the basis to ensure a safe production environment for filling sterile drugs. The filling technology provides for the precise dosing of drug products under the aspect of sterile product handling. Optima Group Pharma unites the required clean room technology with the state-of-the-art filling technology to help you market a high-value pharmaceutical product.



Environmental monitoring check.

The Optima Group Pharma lines cover the entire spectrum from the high-performance segment to the processing of small batches in both the syringe and the vial/infusion bottle area. The advantage for the customers is that they can choose a suitable configuration for their requirements from modularly designed standard machines.

The fully automatic filling and closing machines. Modular and compact designed machines according to cGMP standards with a minimum space requirement – the fully automatic Inova filling and closing machines are applicable for a wide variety of applications, are designed for your individual needs and can be easily retrofitted.

Optima Group pharma's expertise for cGMP-conforming pharmaceutical lines, complete lines, and line supplements cover cleaning, sterilizing, filling, post-processing and handling of syringes, vials and carpules. Our products and services are supplemented by packaging solutions for new pharmaceutical forms and applications and innovative special machines.

Patheon Inc.

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Durham, NC 27703-8580
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fax 919.474.2269
www.patheon.com

Patheon Inc. (TSX: PTI) is a leading global provider of contract development and manufacturing services to the global pharmaceutical industry. The company provides the highest quality products and services to approximately 300 of the world's leading pharmaceutical and biotechnology companies. Patheon's services range from preclinical development through commercial manufacturing of a full array of dosage forms including parenteral, solid, semi-solid and liquid forms. Patheon uses many innovative technologies including single-use disposables, Liquid-Filled Hard Capsules and a variety of modified release technologies.

Patheon's comprehensive range of fully integrated Pharmaceutical Development Services includes preformulation, formulation, analytical development, clinical manufacturing, scale-up and commercialization. Patheon can take customers direct to clinic with global clinical packaging and distribution services and Patheon's Quick to Clinic™ programs can accelerate early phase development project to clinical trials while minimizing the consumption of valuable API.

Patheon's integrated development and manufacturing network of 10 facilities, eight development centers and one clinical trial packaging facility across North America and Europe, ensures that customer products can be launched with confidence anywhere in the world.

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Bethesda, MD 20814
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www.pdatraining.org

Our mission at the **PDA Training and Research Institute (PDA TRI)** is to establish and provide unprecendented worldwide education, training and research opportunities in pharmaceutical and biopharmaceutical sciences and associated technologies. We provide hands-on, intensive, job-focused training you can bring home and apply immediately on the job.

Our broad curriculum is designed for you to enhance your professional development in *aseptic processing, biotechnology, environmental monitoring, filtration, microbiology, quality/regulatory affairs, training, validation and more.* Training courses are held at the PDA TRI facility in Bethesda, Maryland, throughout the United States, and around the world. Courses can also be tailored and brought directly to your organization for on-site training.

Our state-of-the-art training facility includes:

- An aseptic processing suite containing
  - Component prep lab
  - Gowning/degowning areas
  - Clean staging area
  - Filling room
- Biotech lab
- Clean-in-place lab
- Microbiology lab
- Classrooms and student work areas

We have a well-equipped training facility which includes:

- A Fedegari air overpressure/saturated steam autoclave
- Filling line
- Bioreactors/fermenters
- CIP skid
- Continuous particle monitoring system/viable air monitoring
- Laminar flow hoods
- Biosafety cabinets
- Visual inspection booths
- Incubators
- Syringe filler

Our facility is available for your use. TRI makes its training facility available for your use for customized research projects. In addition, we can custom develop any of our training courses to meet your specific needs, either at the Bethesda, MD facility or at your site.

At PDA TRI, we provide skills that can be applied the next day!

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TruCLEAN™ Pro

The TruCLEAN™ Pro captures and isolates contaminants, ensuring delivery of unadulterated cleaning and sanitizing agents. No more re-applying dirty water or weakened solutions, experienced with old-style mopping supplies. TruCLEAN™ Pro is compatible with gamma, ETO and autoclave sterilization. Available in double or triple-bucket design.

TruCLEAN™ II

Our unique bucket-in-bucket concept works to isolate soiled contaminants from cleaning and disinfecting agents. Avoid high costs and risk of run-off contaminants common with steam-sterilizers. TruCLEAN™ Components are constructed of high-grade stainless steel, easy to maintain and guaranteed to deliver reliable cleaning results time after time. Clean floors, walls and ceilings with this efficient, compact mopping system. Compatible with gamma, ETO autoclave sterilization.

TruCLEAN™ Sponge Mops

Designed specifically for use in cleanroom and sterile environments, the TruCLEAN™ Sponge Mop is ideal for applying disinfectants and sterilants. This specially formulated polyurethane foam has excellent chemical, microbial and abrasion resistance. TruCLEAN™ Sponge will not release liquids until pressure is applied. Sponge can hold up to 5 times its weight in liquids.

TruCLEAN™ Microfiber Mops

Introducing our line of TruCLEAN™ Microfiber Mops, the most environmentally friendly, non-chemical tool on the market for today's cleaning industry. Our Microfiber Mops can absorb up to 7 times their weight in liquids and can be re-used up to 500 times. Compatible with gamma, ETO autoclave sterilization, also launderable.

PERFEX Squeegees

Our Twin-Blade and Quick-Dry Foam Squeegees are chemically resistant and non-sparking, will not rust or corrode. Quickly wipe surfaces dry and nearly streak-free. Ideal for floor chemical application. The squeegees 100% polymer construction will resist water, oil, grease, detergents, sanitizers and solvents. Wash and rinse with warm water, dries quickly.

PERFEX Push Brooms

Polypropylene fibers are fused onto high-impact resistant polymer block, eliminating fiber fallout. Perfex color-coded brooms, brushes and handles will not absorb bacteria, liquids or odors and are unaffected by water, grease, petroleum products, detergents, sanitizers and solvents. Help avoid cross-contamination in your facility by using Perfex brooms, brushes and handles.

Pharma Tech Industries

545 Old Elbert Rd.
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tel. 706.246.3555
fax 706.246.3330
www.pharma-tech.com

Powder Manufacturing/Packaging

PTI has extensive experience in blending both oral (ingestible) and topical powder formulations and can manufacture, formulate and package effervescent products, as well. Our packaging capabilities include bottle filling (high speed powder bottle filling, capping, sealing, coding and bundling); pouch (unit dose) filling (high speed/precision powder filling into a sachet or pouch); cartoning (on-line or off-line), labeling and custom packaging.

Solid Dose and Effervescent Manufacturing/Packaging

PTI has the capability to manufacture both single and bi-layer pills and can package virtually any type of pharmaceutical or over the counter product, including high speed/precision tablet filling into a sachet or pouch, as well as coding and/or cartoning.

Injection Molding

PTI has a dedicated machine shop and tool rooms for mold design and refurbishment to mold bottles, caps, components, and devices for both in-house and external packaging components. PTI's molding capabilities include injection blow-molding, single and two component injection molding, compression molding and profile extrusion.

Clean Rooms

PTI offers seven ISO 8 Level (Class 100,000) clean rooms in order to handle its growing pharmaceutical business. The specially engineered rooms have highly sensitive control features to closely regulate and monitor both temperature and humidity.

Custom Manufacturing/ Packaging

PTI has the expertise to implement and design custom manufacturing and packaging tailored to our clients needs. Our team will work with your experts to collaborate on an innovative product and packaging solution that meets your cost and quality objectives.

Technology Transfer

From product development to commercial execution, our goal is to help pharmaceutical packaging marketers save both time and money with our unique solutions. PTI offers expertise in technology transfers of late stage R&D, dedicated operations (large and small scale), niche processes and transfers to PTI's turn-key approach through vertical integration.

Pharmaceutical Technology

www.PharmTech.com

Corporate Description

For more than 30 years, *Pharmaceutical Technology* has published authoritative, reliable, and timely information on every aspect of applied pharmaceutical science and biotechnology. More than 38,000 professionals rely on *Pharmaceutical Technology* to stay ahead of the curve in manufacturing equipment and processes, formulation and drug delivery, active pharmaceutical ingredients and excipients, software and automation, validation and compliance, packaging and labeling, outsourcing issues, and a host of related topics. The industry's premier editorial staff delivers unequaled double-blind, peer-reviewed research, authoritative technical articles, independent news reports, and in-depth staff analyses.

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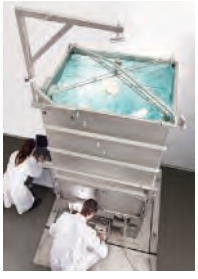


Flexel® for Magnetic Mixing

Flexel for Magnetic Mixing is designed for single-use aseptic mixing in process development and manufacturing applications from 50L to 2,500L. It is ideal for biopharmaceutical processes requiring powerful mixing torque, such as buffer and media preparation, product resuspension and homogenization applications. It offers proven scalable and ready-to-use mixing technology to enhance process flexibility and optimize manufacturing costs. Website: http://www.sartorius-stedim.com/magnetic-mixing

UniVessel® SU

The first completely Single-Use Bioreactor for Lab Scale, Cell Culture and Process Development. Applications range from small-scale, protein expression to media or process optimization studies. UniVessel SU works with most benchtop controllers for conventional, stirred-tank glass bioreactors. The pre-assembled system eliminates the need for cleaning and autoclaving and decreases the risk of contaminations.

Sartopore® 2 XLM 0.1 µm

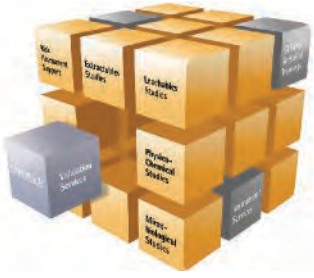
Sartorius Stedim Biotech's next-generation 0.1-µm PES Mycoplasma retentive Filter. Sartopore® 2 XLM combines Highly Asymmetric 0.2-µm Prefilter layer with Mycoplasma retentive to LRV= 7/cm2, 0.1-µm final membrane – the same as its predecessor - Sartopore® 2 0.2/0.1. XLM's 30% increase in EFA to 0.8 m2/10" leads to 1/3-1/2 less 10" elements to process the same batch.

Sterisart® Universal Pump

The Sterisart Universal Pump is a peristaltic pump made of stainless steel, equipped with appropriate features for attaching a closed sterility test system and a sample container. Its low, compact design has a space-saving footprint – a great benefit for most cleanroom benchtops and isolators.

SARTOFLOW® Advanced

SARTOFLOW Advanced is a flexible crossflow system designed for use in laboratory environments for process development and clinical trial material preparations, as well as for small-scale production batches. It is a modular, benchtop system optimized for ultrafiltration, microfiltration and diafiltration applications - common operations in many downstream processes for the purification of vaccines, monoclonal antibodies and recombinant proteins.



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Sartorius Stedim Biotech's Validation Services provides extractable and leachable testing that is designed to meet current regulatory requirements. Our recommended approach includes the use of at least two orthogonal analytical techniques — for example, GC-MS in addition to HPLC-UV. Let us help you implement a successful test strategy. Contact us today!

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New Stericlean Robot

Thanks to its experience in the field of Life Science and the requirements of a leader in the Pharmaceutical industry, Stäubli has adapted its range of well known CLEANROOM industrial robots to meet the stringent requirements of the Vapor Hydrogen Peroxide decontamination process.

Stericlean Robot Highlights:

- Fully hydrogen peroxide (H202) resistant robot
- Robot arm suitable for decontamination process in VHP environments
- Human arm like automated operator in isolator environment (glove box)
- Reliability proven by the leaders in life science and Cleanroom

Stericlean Robot Technical features:

- Special surface treatments of the TX 60 Stericlean robot arm
- Critical parts in stainless steel
- Specific lip seals
- System and user connections protected under the base of the robot
- Small footprint with large work envelope
- GMP (Good Manufacturing Processes) qualified

Stericlean applications:

- Pharmaceutical Industry, Life Science, and Medical Technology industries
- Lab operations
- Batch testing
- Production
- Drug discovery

TX Stericlean was born from a strong relationship between Stäubli, a system integrator and our end user. These committed partners share the same strategies and bring to the table experience in robotics, automation processes and “clean room” environments.

Whether in industrial production, cell culture or medical preparation, this new technology has demonstrated its ability to simulate human motion and meet productivity goals, significantly raising the rate at which syringes can be filled on a high-speed line.

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Accurate Control for Sanitary Systems

The RHPS series PRSTC model springloaded, pressure-reducing regulators offer accurate control of gas and liquid pressures in sanitary systems. Inlet pressures as high as 230 psig (16 bar) can be controlled to outlet pressures ranging from 4.3 to 130 psig (0.3 to 9 bar). Operating temperature range is -31° to 284°F (-35° to 140°C). Three body sizes are available: 1/2, 1, and 1 1/2 in., all with integral sanitary clamp end connections. Flow coefficients (C_v) are 0.70 (1/2 in.), 1.95 (1 in.), and 5.48 (1 1/2 in.). Designed for clean service, regulator internal surfaces are finished to 16 µin. (0.4 µm) R_a standard.

Tankblanketing Applications

RHPS series TBRS and TBVS model regulators provide accurate pressure control in low-pressure gas systems, including blanketing gas in a closed tank or vessel. Installed on a tank's inlet and outlet, the TBRS (inlet) and TBVS (outlet) regulators maintain a tank's blanketing gas at a constant pressure. Operating temperature range is -4 to 280°F (-20 to 140°C). Sizes range from 1/2 to 2 in. End connections include NPT female, BSP parallel female, ANSI 150# flanges, DIN DN25 PN 16 flanges, or sanitary tri-clamp. Regulators are ultrasonically cleaned and degreased. Cleaning based on ASTM-G93 Level C/CGA 4.1 is available.

High Flow Requirements

RHPS series domeloaded pressure regulators permit high flows while controlling the pressure of liquids and gases. Inlet pressures can range to 5800 psig (400 bar). Available for pipe sizes ranging from 1/4 to 4 in. with corresponding C_v values ranging from 0.1 to 73. End connections include NPT female, BSPP female, and ANSI and DIN flanges. Body, dome, and trim material for all models is 316L stainless steel. Operating temperatures range from -4 to 176°F (-20 to 80°C). Larger models include an integral pilot regulator to keep dome pressure constant.

Thomas Engineering

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Thomas Engineering is proud to offer the new Accela-Cota® FLEX 500, the industry's only production class batch tablet coater with 7 exchangeable drums. Designed to increase tablet coating productivity while maintaining product quality, consistency and process reliability, the FLEX 500 is the manufacturing solution for any of your tablet coating needs.

The FLEX 500 has a unique combination of features to help reduce down time for batch-to-batch change over, giving the coater more process time to coat tablets – enhanced utilization, higher throughput, better profit!

With almost limitless possibilities, the FLEX 500 is the preferred choice for processing tablets using film, sugar, functional, and drug layer coatings. Built for today's needs – adaptable for tomorrow's.

For more information about the Thomas Engineering Accela-Cota® FLEX 500 and many more tablet coating solutions please visit us at www.thoamseng.com or call 800.634.9910.

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The "SimpleMIX System" eliminates filter sterilizing of disinfectants and sporicides. A sealed multichamber container mixes both solutions. The top part contains the sterile concentrated disinfectant, and the bottom section accommodates the sterile USP water-for-injection-quality water. This system ensures the appropriate dilution is made in a closed sterile system each time.

Peracetic acid

Veltek offers the "DECON SPORE 200 Plus" peracetic acid–hydrogen peroxide solution for the sterilization of manufacturing, packaging, and filling equipment. The product has less odor than ready-to-use sterilants and requires 80% less storage space. It is available in 1-gal containers, unit-dose bottles, and in the "SimpleMix" system.

Hands-free dispensing system

Veltek offers the "Asepti Cleanse Hands-Free" dispensing system to dispense sterile alcohol and hand sanitizer. The Asepti Cleanse system is a sealed, water-resistant unit designed to meet the requirements of cleanroom operations. The unit can be powered by either four D-cell batteries or connected directly to a 110-V power source.

Easy2Gown System

Veltek Associates, Inc.'s Easy2Gown garments offer an innovative fold which allows the gown to be easily donned with virtually no operator contact with the outside of the gown. All Easy-2Gown garments are packaged using a unique patented fold which was developed to minimize operator error and personal contact from the outside of the gown during the gowning process. Operators have fewer manipulations while donning the Easy2Gown garments.

Cage2Wash®

Cage2Wash products have been specifically designed for critical animal facility component and animal cage washing applications. In this venue, the appropriate use of a cleaning agent to remove animal waste and animal by products is critical.

Process2Clean®

Process2Clean products have been specifically designed for critical clean in place applications. In this venue, the appropriate use of clean in place cleaners warrants two concerns. The first concern relates to the ability of the specific detergent to remove existent product residues that may exist in either open or closed processes manufacturing equipment and vessels. The second concern is the ability to rinse free the product residue, P2C addresses both concerns with ease.

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Weiler Engineering, Inc.

The corporate focus of Weiler Engineering, Inc. is to provide the most advanced aseptic liquid processing technology available through the application of customized ASEP-TECH® Blow/Fill/Seal machinery and integrated services. Weiler's 140,000 ft², state-of-the-art manufacturing and corporate facility is conveniently located near O'Hare International Airport in Chicago, IL USA.

ASEP-TECH® Model 624 Blow/Fill/Seal Machine

The Asep-Tech® Model 624 Blow/Fill/Seal machine is designed as an entry level machine to meet flexible manufacturing or research and development requirements. Featuring easy maintenance and low operating cost, the versatile Model 624 can produce sterile, liquid filled, tamper-evident containers ranging in size from 0.5mL up to 500mL.

ASEP-TECH® Model 628 All-Electric Blow/Fill/Seal Machine

Weiler Engineering, Inc. introduces the new all-electric version of the popular Model 628 Blow/Fill/Seal machine. The all-electric model offers the ultimate in clean, green processing, minimizing the carbon footprint and enhancing the quality of the processing environment through highly reduced particulate generation. The all-electric option is ideal for injectable product applications.

ASEP-TECH® Model 640 Blow/Fill/Seal Machine

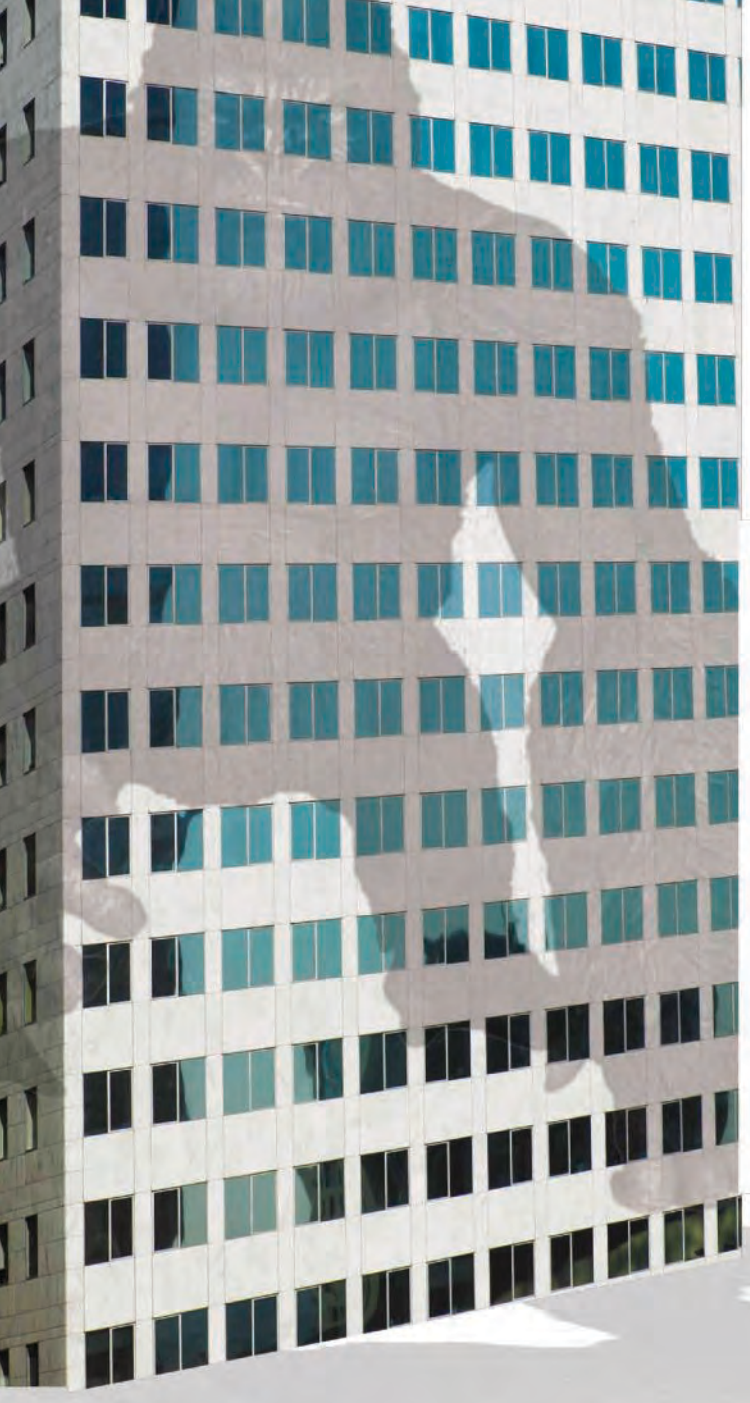
The high output Model 640 machine is designed for maximum flexibility to meet today's demanding FDA and EU processing requirements. It features a two-piece stepped base to facilitate easy maintenance and comes with an electronic fill system and digital controls to enable performance to tight fill tolerances in critical applications.

ASEP-TECH® Model 603 Blow/Fill/Seal Machine

The Asep-Tech® Model 603 Blow/Fill/Seal machine is designed for production of Large Volume Parenteral products (LVPs). It features a two-piece stepped base design for easy maintenance and convenient product discharge and is designed to produce sterile, liquid filled, tamper-evident containers ranging in size from 200mL up to 1000mL, in full-scale production quantities.

ASEP-TECH® Model 660 Blow/Fill/Seal Machine

The Asep-Tech® Model 660 Blow/Fill/Seal machine is the latest addition to a proven line of sterile liquid pharmaceutical packaging machines from Weiler. The Model 660 is a high-output machine, designed to produce sterile, liquid filled, tamper-evident containers ranging in size from 200mL up to 1000mL.



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MANUFACTURING EQUIPMENT & SUPPLIES

Rheometer

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Aseptic liquid-sampling system

GEMÜ offers a fully automatic aseptic sampling system for liquids and pure steam. The system is appropriate for mobile or fixed installation. It features sterile sampling and transport and programmable automation for customer-specific variables. The closed system protects personnel and uses compressed air as cooling and condensing media. **GEMÜ Valves and Instrumentation,** *Atlanta, GA • www.gemu.com • tel. 404.344.8970*

Filter-integrity tester

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

MANUFACTURING EQUIPMENT & SUPPLIES

Pharmaceutical robot

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

Tablet-coating platform

The Accela-Cota FLEX 500 tablet-coating platform features seven exchangeable drums and provides a batch-size range of 50–920 L. Innovative gun positioning, a segmented exhaust plenum, and interchangeable mixing baffles configure the coater according to the requirements of the batch size and coating processes. **Thomas Engineering,** *Hoffman Estates, IL • www.thomaseng.com • tel. 800.634.9910*

Light-induced fluorescence sensor

Natoli's Light-Induced Fluorescence (LIF) sensor was designed for blend uniformity and end-point detection during the blending of powders, as well as for liquid applications, including cleaning validation. The advanced technology of the LIF Sensor enables real-time monitoring of fluorophore solutes through intrinsic fluorescent sensing in the solid state. **Natoli Engineering Company,** *St. Charles, MO • www.natoli.com • tel. 636.926.8900*

MANUFACTURING EQUIPMENT & SUPPLIES

Weigh pan

The SmartGrid weigh pan is designed for Mettler Toledo's Excellence balances. The weigh pan is designed to minimize the effects of air turbulence for faster stabilization. Users can secure fastening and direct weighing into tare containers with Ergoclips. The unit is intended to provide quality and durability. **Mettler Toledo,** *Columbus, OH • www.mt.com • tel. 800.METTLER*

FETTE COMPACTING AMERICA

Validation and documentation

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

Turnkey vial line

Optima Group Pharma offers a turnkey processing line for vials that comprises an integrated freeze-drying system. Designed to be flexible and operator-friendly, the line processes liquids, freeze-dried pharmaceuticals, and biopharmaceuticals. **Optima Group Pharma,** *Green Bay, WI • www.optima-pharma.com • tel. 920.339.2222*

MANUFACTURING EQUIPMENT & SUPPLIES

Tablet press

The new model of the Hata CVX Core Press enables precision core alignment and multilayer core tableting. The custom mechanical assembly, an addition to Hata's Three-Layer Tableting Press, is specific to customers' core tablet sizes and shapes. The CVX-Series is suitable for multilayer and custom core-tableting technology. **Elizabeth-Hata,** *McKeesport, PA • www.eliz.com • tel. 412.751.3000*

Blow–fill–seal machine

The Asep-Tech Model 628 blow–fill–seal machine from Weiler features a two-piece stepped base design to facilitate maintenance and product discharge. Model 624 tooling can be used on the Model 628 machine. The Model 628 unit produces sterile, liquid-filled, tamper-evident containers ranging in size from 0.5 mL to 250 mL. **Weiler Engineering,** *Elgin, IL • www.weilerengineering.com • tel. 847.697.4900*

Handheld analyzer

Thermo Scientific's TruScan RM unit is a handheld analyzer designed for rapid identification of raw materials and finished-product inspection. The instrument weighs less than 2 lb. and delivers results five times faster than the previous model. A new optical platform enables the TruScan RM unit to identify a broader range of chemical compounds. **Thermo Scientific,** *Wilmington, MA • www.thermoscientific.com • tel. 978.642.1132*

MANUFACTURING EQUIPMENT & SUPPLIES

Automated sampling system

Allegheny Bradford designed its Automated Sampling System to be easy to install, operate, and maintain. The system's continuous-flow design ensures constant sterility that supports cleaning and steaming in place. The unit includes a double-tubesheet heat exchanger for leak detection and Pitot–Venturi tube design. **Allegheny Bradford,** *Lewis Run, PA • www.alleghenybradford.com • tel. 800.542.0650*

Regulators for pharmaceutical systems

Swagelok's RHPS PRSTC model spring-loaded, pressure-reducing regulators offer accurate control of gas and liquid pressure in pharmaceutical systems. The regulators are available in three body sizes, feature 316-L stainless-steel construction, and include integral sanitary clamp end connections. All regulators are 100% factory tested, ultrasonically degreased, and cleaned. **Swagelok,** *Solon, OH • www.swagelok.com • tel. 440.349.5934*

Cylindrical blender–dryers

Ross's cylindrical blender–dryers are suitable for high-temperature processing of slurries, pastes, granular materials, pellets, and powders under vacuum, atmospheric, or positive pressure. The machines are custom built to meet users' needs and available in sizes from 0.5- through 515-ft^3 capacities in industrial or sanitary construction. **Ross, Charles & Son Company,** *Hauppauge, NY • www.mixers.com • tel. 800.243.ROSS*

MANUFACTURING EQUIPMENT & SUPPLIES

Membrane filter cartridges

Meissner offers a brochure describing its EverLUX PES membrane filter cartridges. The hydrophilic filters are designed for high contaminant capacity, extended service life, and high flow rates when filtering various biological fluids. The brochure includes a typical water-flow rate chart to provide sizing guidelines for flow requirements. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Culturing set

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

Quality-control system

The FS-80 IP system reliably detects improperly sealed cans and twist-off bottle caps. The system improves final-product quality on assembly lines that fill containers under vacuum or pressure, including nitrogen-dosed cans, and it reliably detects low vacuum or pressure at speeds as high as 1300 bottles/min or 2000 cans/min. **Industrial Dynamics/filtec,** *Torrance, CA • www.filtec.com • tel. 888.434.5832*

MANUFACTURING EQUIPMENT & SUPPLIES

Fluid-bed dryer bags

Kavon provides custom replacement fluid-bed dryer bags for US and European equipment models. The bags are appropriate for wet granulation, dry filtration, and wet and dry coating applications. The company offers flexible 1–4-bag systems in various fabrics choices and also repairs bags.
Kavon Filter Products, *Wall Township, NJ • www.kavonfilter.com • tel. 732.938.3135*

Detergents

Alconox detergents are designed to handle tough crucial cleaning jobs from tablet presses to mixing tanks. The Alconox product is a concentrated, anionic detergent for manual and ultrasonic cleaning. It is suitable for cleaning contaminants from glassware, metals, plastic, ceramic, porcelain, rubber, and fiberglass. The solution is intended to replace corrosive acids and hazardous solvents. **Alconox,** *White Plains, NY • www.alconox.com • tel. 914.948.4040*

Visual-observation tool

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

OUTSOURCING & CONSULTING SERVICES

Metrics INC.

Contract services

Metrics is a respected contract pharmaceutical research, formulation, development, and manufacturing company. Offering first-in-man (FTIM) development and Phase I–III clinical-trial materials (CTM), Metrics has conducted more than 120 FTIM studies for various chemical entities in the past five years while producing more than 700 batches of CTM. **Metrics,** *Greenville, NC • www.metricsinc.com • tel. 252.752.3800*

Bioanalytical analysis

MPI's senior scientists develop and validate assays to support development from preclinical to Phase I–IV clinical research. The company's specialized capabilities include mass spectrometry of small molecules, proteins, peptides, thermal analysis, immunochemistry, and residue analysis (including independent laboratory validations for crop protection and method trials for animal health). **MPI Research,** *Mattawan, MI • www.mpiresearch.com • tel. 269.668.3336*

Contract services

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

OUTSOURCING & CONSULTING SERVICES

PDA Parenteral Drug Association
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Job-focused training

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

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Hospira's One 2 One business is a leading contract manufacturing organization specializing in injectable fill–finish services. The company meets clients' global manufacturing and supply demands with lyophilization capabilities at its three facilities located in Kansas, Milan, and Melbourne. **Hospira One 2 One,** *Lake Forest, IL • www.one2onecmo.com • tel. 224.212.2267*

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Lancaster Laboratories, a global leader in comprehensive laboratory services, enables pharmaceutical and biopharmaceutical companies to advance candidates from development through commercialization and ensures regulatory compliance, cost effectiveness, and the achievement of timelines. The company offers five service models, including fee-for-service, full-time-employee, and Professional Scientific Staffing.
Lancaster Laboratories, *Lancaster, PA • www.lancasterlabs.com • tel. 717.656.2300*

OUTSOURCING & CONSULTING SERVICES

Pharmaceutical services

WellSpring Pharmaceutical is a full-service provider of clinical and commercial manufacturing and packaging, blinding, method development, analytical testing, and distribution services. Highly qualified managers and technical professionals work at the company's 100,000-ft² facility to ensure that clients' clinical and commercial products meet high standards. **WellSpring Pharmaceutical Canada,** *Oakville, Canada • www.wpcoutsourcing.com • tel. 866.337.4500*

Manufacturing and packaging services

Pharma Tech Industries offers a brochure that describes its pharmaceutical manufacturing and packaging services, its facilities in Georgia and Missouri, and its technical capabilities. The brochure also includes customer testimonials from global pharmaceutical leaders and photos of its facilities, machinery, and dedicated employees. **Pharma Tech Industries,** *Royston, GA • www.pharma-tech.com • tel. 706.246.3555*

CLEANROOM EQUIPMENT & SUPPLIES

Sterile wipes

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

CLEANROOM EQUIPMENT & SUPPLIES

Microfiber mops

Perfex offers a line of TruCLEAN microfiber mops, which are nonchemical cleaning tools designed to be environmentally friendly. The microfiber mops can absorb as much as seven times their weight in liquids and can be reused as many as 500 times. The washable products are compatible with gamma irradiation, ethylene oxide, and autoclave sterilization. **Perfex,** *Poland, NY • www.perfexonline.com • tel. 800.848.8483*

PACKAGING EQUIPMENT & SUPPLIES

Transfer packaging for prefillable syringes

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

Packaging solution

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

LABORATORY EQUIPMENT & SUPPLIES

Analytical system

The amaZon PowerPack liquid chromatography–mass spectrometry system combines the performance and reliability of the amaZon SL ion-trap mass spectrometer with a state-of-the-art Dionex UltiMate 3000 ultrahigh-performance liquid chromatography system. The instrument is designed to enhance the analytical capabilities and productivity of laboratories that analyze the structure of various molecules. **Bruker Daltonics,** *Billerica, MA • www.bdal.com • tel. 978.663.3660*

Analytical system

Waters' Acquity ultraperformance supercritical-fluid chromatography (SFC) system combines the advantages of sub 2-µm particle technology and the efficiency of SFC. This system reduces run times by as much as 10 times, reduces solvent usage as much as 95%, and cuts the cost of analyses by as much as 99%. The technique is a green alternative to normal phase chromatography for chiral and achiral separations. **Waters,** *Milford, MA • www.waters.com • tel. 508.478.2000*

Process-analysis system

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

LABORATORY EQUIPMENT & SUPPLIES

Total-organic-carbon analyzer

The Anatel TOC600 on-line total-organic-carbon analyzer is designed for pharmaceutical water measurement. Its patented stop-flow oxidation technology provides complete oxidation of an aliquot of water and fully complies with *USP* <643> and *EP* 2.2.44. The Anatel TOC600 unit's wide dynamic range allows for monitoring an array of water-system applications. **Hach Ultra Analytics,** *Grants Pass, OR • www.hachultra.com • tel. 541.472.6500*

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*

Laboratory blenders

MaxiBlend and MiniBlend laboratory blenders are available in sizes from 0.5 to 16 qt. The units are made of 316-L stainless steel and supplied with V-shells, bins, or double cones. The units feature a tabletop design and include programmable logic controls and safety-interlocked guards. **GlobePharma,** *New Brunswick, NJ • www.globepharma.com • tel. 732.819.0381*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

Pharmaceutical polymers

EUDRAGIT acrylic polymers are designed for enteric, sustained-release, and immediate-release drug-delivery formulations of solid oral dosage forms. Evonik's portfolio of development services ranges from formulation support to individually designed drug-delivery technologies. **Evonik Degussa Corp., Pharma Polymers,** *Piscataway, NJ • www.eudragit.com • tel. 732.981.5383*

Pharmaceutical chemicals

Avantor Performance Materials (formerly Mallinckrodt Baker) has renamed its Mallinckrodt Chemicals product line Macron Chemicals. The name change does not involve any product or manufacturing changes. The Macron Chemicals product line is identical to the previous Mallinckrodt line and includes high-purity solvents, acids, salts, minerals, and sugars. **Avantor,** *Phillipsburg, NJ • www.avantormaterials.com • tel. 855.AVANTOR*

High-purity inorganic salts

Jost Chemical has manufactured high-purity inorganic salts for 25 years. Jost's FDA-registered site in St. Louis, Missouri, includes 190,000 ft^2 and operates under current good manufacturing practice for bulk pharmaceuticals. Jost is a global supplier of chemical salts that meet compendial requirements, and the company tests its products in house. **Jost Chemical,** *St. Louis, MO • www.jostchemical.com • tel. 314.428.4300*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

Ingredients catalog

Spectrum's 2012–2013 bulk fine chemicals and intermediates catalog contains more than 3300 products for scale-up and production, including a comprehensive selection of *US Pharmacopeia*-grade chemicals. The company's custom synthesis and manufacturing capabilities for active pharmaceutical ingredients and controlled substances are also highlighted in this reference handbook. **Spectrum Chemical Manufacturing,** *Gardena, CA • www.spectrumchemical.com • tel. 800.901.5516*

INFORMATION TECHNOLOGY

Materials-identification database

The PDF-4/Organics 2011 database, featuring 436,901 entries, is designed for rapid materials identification and targeted to the pharmaceutical and specialty-chemical industries. Its design allows for easy interface with diffractometers and data-analysis systems of leading software developers and manufacturers of X-ray equipment. The database is useful for scientists working in consumer products, catalysis, forensic science, analytical laboratories, and production. **International Centre for Diffraction Data,** *Newtown Square, PA • www.icdd.com • tel. 610.325.9814*

Compliance software

EtQ's FDA Compliance Management software is an integrated quality- and compliance-management system designed to maintain compliance to various regulatory requirements and adapt to business processes. EtQ's modules are tightly integrated to deliver a high-quality FDA-compliance solution and include MedWatch Plus, Complaint Handling, Corrective And Preventive Action, Document Control, and Change Management. **EtQ,** *Farmingdale, NY • www.etq.com • tel. 800.354.4476*

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OUTSOURCING RESOURCES

CENTRIFUGES

CHEMICALS/EXCIPIENTS/API'S

Bulk Oils

LAB EQUIPMENT

Airflow Diagnostic Tools

MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

OUTSOURCING RESOURCES

Analytical Testing

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two hours, and only 43% could obtain the information within a business day.

Potential solutions

This lack of visibility supports the need for the implementation of data acquisition and analytic systems and processes that can help provide on-demand visibility across a company's supply chain. Such information would afford a sponsor company the opportunity to better and more tightly control ingredients, components, and products supplied by third parties. Because brand owners are responsible for the safety, efficacy, and quality of their products, this control is crucial and can help manage and reduce the risk of nonconformances, corrective and preventive actions, and product recalls.

To address the challenges of globalization and outsourcing, companies must implement strategies to provide appropriate levels of visibility across every stakeholder in their supply network.

The willingness of partners to share information was a top issue uncovered by Axendia's research. When asked, "What are your organization's concerns regarding increased regulatory focus on global supply-chain issues?" nearly 60% said they are concerned about the willingness of suppliers to provide information. Forty-four percent are concerned about their distributors' willingness to provide information required to meet regulatory requirements.

This information would ensure that organizations can support the full genealogy and traceability of their products, from raw materials to end users. The willingness of suppliers and contract organizations to provide that information is imperative to achieving this goal. It is not enough to look at the first link in the chain. In an age when contract organizations are also outsourcing, the supply chain is even longer and more difficult to assess. Brand owners, therefore, must go further into their supply chains to assess distributors as well as suppliers to their suppliers. Such visibility would enable downstream processes (whether local, global, or outsourced) to adjust CQAs and CPPs to compensate for product characteristics.

Today, there is mature technology available to support the implementation of interconnected and interoperable systems that provide on-demand-visibility across the supply network. This level of transparency would not only support PAT and QbD approaches, but also would manage product safety, efficacy, and quality. **PT**

Reference

1. M. Hamburg, Testimony before the US House Subcommittee on Oversight and Investigations, Apr. 13, 2011, www.fda.gov/NewsEvents/Testimony/ucm250710.htm.
2. Axendia Research Report, "Achieving Global Supply Chain Visibility, Control & Collaboration in Life Sciences: Business Imperative, Regulatory Necessity," 2010, www.axendia.com/2010_LS_GSC.html. **PT**

For more data on the effect of globalization and outsourcing on the pharmaceutical supply chain, please see PharmTech's August 2011 Outsourcing Resources special issue.

Ad Index

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Has Outsourcing Derailed PAT and QbD?

Daniel R. Matlis

Managing knowledge and monitoring quality require more effort in a complex supply chain.

In the days when pharmaceutical companies were vertically integrated, industry and regulators began to develop ways to change the paradigm for pharmaceutical manufacturing from "testing quality out" to "building quality in." These collaborations resulted in innovative approaches under FDA's Critical Path Initiative and included process analytical technology (PAT) and quality by design (QbD).

PAT continues to drive industry to gain a deeper understanding of its products and manufacturing processes to allow for tight controls over critical quality attributes (CQAs) and process parameters (CPPs). This approach supports the implementation of control strategies aimed at improving quality while reducing the need for in-process and finished-goods testing. To collect, act, and capitalize on the knowledge gained from identifying and monitoring CQAs and CPPs, many companies have been and continue to invest significant resources in data acquisition, historian, and manufacturing execution systems.

These paradigms were designed to enable life-science organizations to speed time to market, improve quality, and lower costs while facilitating compliance with regulatory requirements.

Daniel R. Matlis is founder and president of Axendia, dmatlis@axendia.com.

The outsourcing effect

The pharmaceutical industry is also increasing its level of outsourcing of non-core activities, processes, and supplies as a means to lower costs. As a result of outsourcing, many brand owners have lost their visibility into CQAs and CPPs. When a company does not own the equipment, it is often difficult to collect, act, and capitalize on indicators and parameters. These data are needed to achieve PAT and QbD, and also have a significant effect on drug product safety, efficacy, and quality.

When you don't own the equipment, it's difficult to act on indicators and parameters.

Despite this problem, globalization and outsourcing are here to stay. According to Congressional testimony given by FDA Commissioner Margaret Hamburg, "up to 40% of the drugs Americans take are manufactured outside our borders, and up to 80% of the active pharmaceutical ingredients in those drugs comes from foreign sources" (1).

According to findings from Axendia's Life-Science Global Supply Chain research, 78% of industry executives expect global sourcing to increase, and 76% anticipate their global manufacturing to grow (2). These executives also reported that they expect the top threats in the next five years to stem from these same trends. While 74% identify contract manufacturing as a "significant or moderate risk," 61% view contaminated or nonconforming raw materials as a top threat.

Today, visibility into the pharmaceutical supply chain is largely based on "snapshots in time" with little sharing of common practices and information. According to Axendia's research, more that three quarters (77%) of industry executives responding to the survey indicated that the primary method used to gain visibility into suppliers is a periodic audit. Only 25% stated that they share common practices and information with suppliers and only 3% said they have real-time access to their suppliers' data.

An audit, although required, provides visibility into a specific timeframe. After an on-site visit, the next time a sponsor company is likely to get data from the contract supplier or manufacturer is either when it receives a batch of product along with some form of document such as a quality certificate or a certificate of analysis.

This lack of visibility is illustrated by the low proportion of survey respondents able to gather critical information across their product supply chain in a timely manner. Only 19% of executives reported that they could obtain needed information from critical suppliers within two hours.

Interconnected systems that enable "on-demand-visibility" (i.e., the ability to obtain relevant product information at the appropriate time to enable decisions with a high degree of confidence) within an organization and its suppliers/contract organizations is also limited. Only 28% of survey participants said they could obtain information from their company sites within

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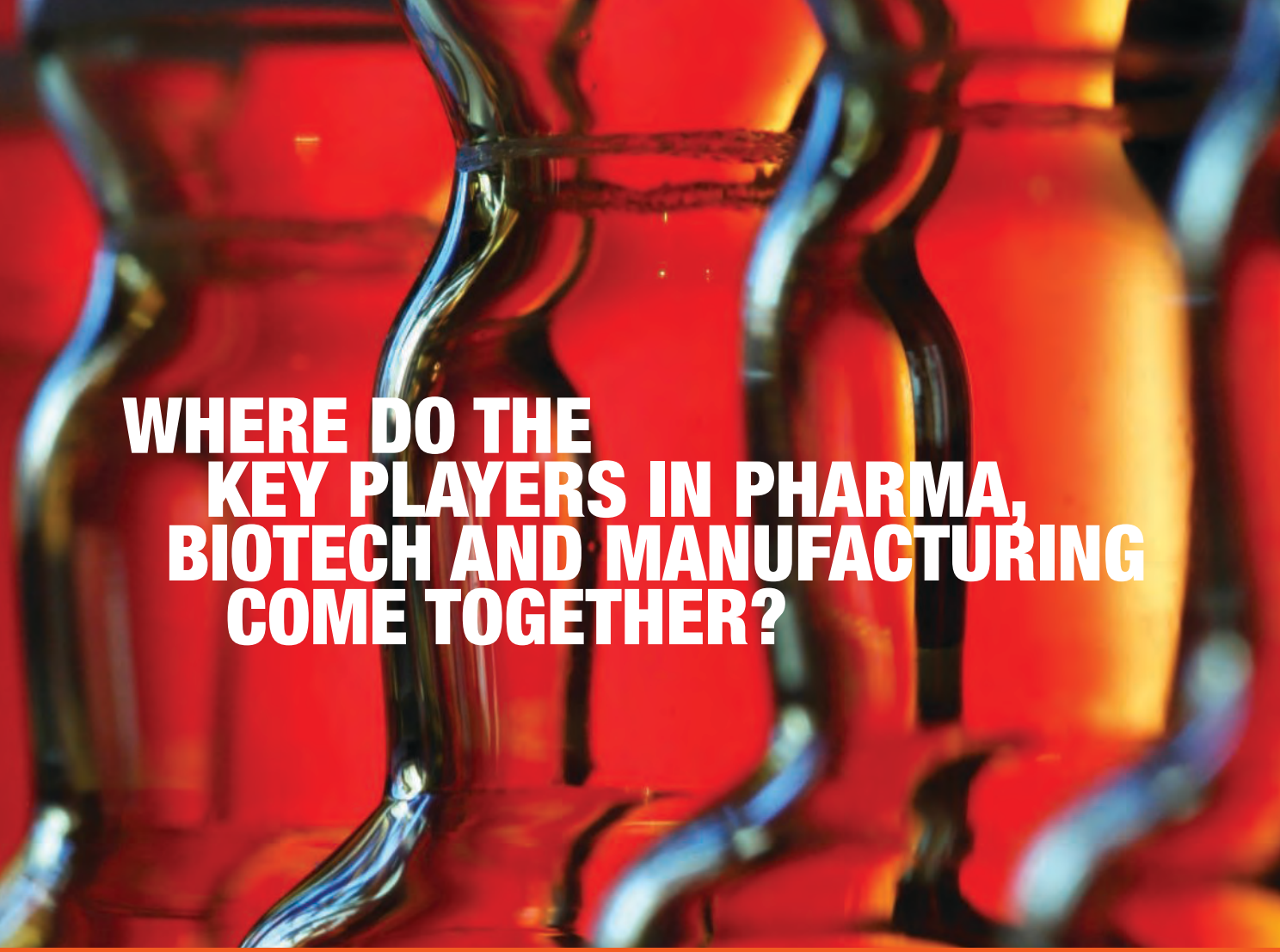

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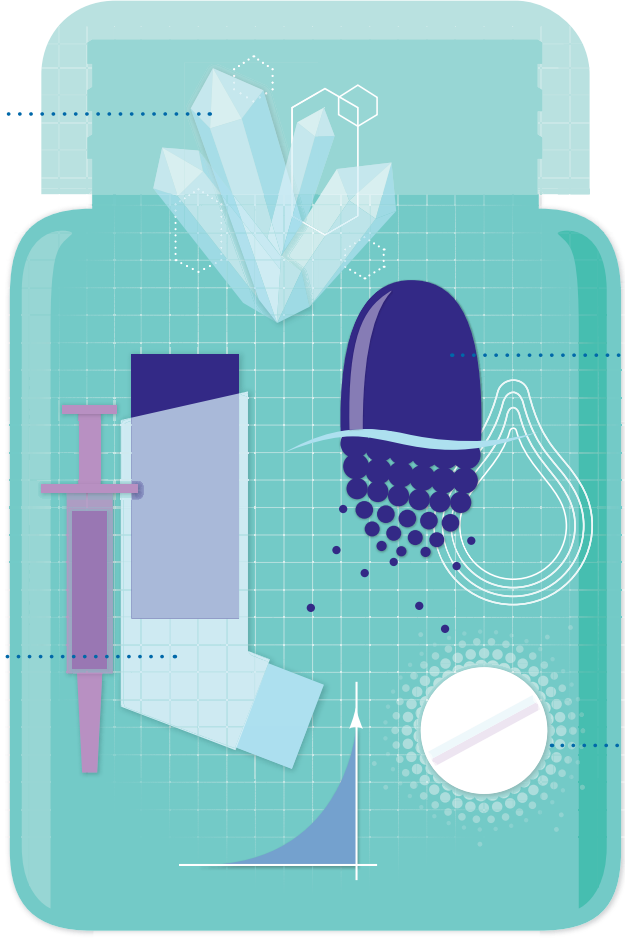

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