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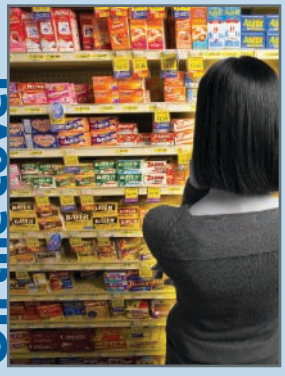

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Issue extra

An expanded version of this month's Packaging Forum includes more INTERPHEX 2011 products, by *Hallie Forcinio*

Web exclusive

A. Mark Trotter reviews An Indispensible Book on Disposables (Wiley, 2011)

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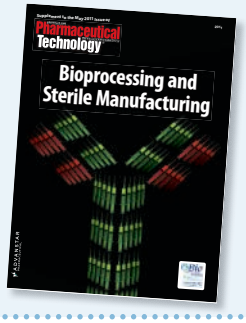
Be sure to check out this month's Bioprocessing and Sterile Manufacturing supplement.



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Perception and Reality

Michelle Hoffman

Those who doubt there's faith in science, should check out our annual Bioprocessing Survey.

If you, like me, were a science student as an undergraduate who had friends in the humanities, you had the inevitable discussion about the objectivity of fact versus the subjectivity of faith.

The scientist would cite the rigor and reliability of the scientific method and the "truth" of reproducible results. The humanities student would argue that the so-called axiomatic truth of the sun rising tomorrow, for example, was just another form of faith. The scientist, argued the humanities student, was operating under the assumption that past behavior was a predictor of future behavior and so believed the sun would rise tomorrow merely because it had every day in the past for eons.

The arguments are not very original, nor are they decisive, and yet they remain with me. Every so often during introspective moments, I subject myself to a sort of epistemological grilling: How do I really know what I think to be true? What data set am I using to reach my conclusions, and how was it generated? And finally, do I believe this to be true because I want it to be, because it's an act of faith or will, or is there really substantial, objective support for this?

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

These are questions I revisit every year when we conduct our annual Bioprocessing Survey, which you can read in this month's special issue on Bioprocessing and Sterile Manufacturing. (Thank you, by the way, to those who took the survey; and for those who did not, there's always next year.) The biopharmaceutical manufacturing sector has over the years been exploring the benefits of single-use, disposable components in its operations versus those of traditional stainless-steel components. Opinions about the relative merits of one kind of equipment over the other abound. And they diverge, depending on whether one actually uses disposables.

Opinions about the relative merits of one kind of equipment over the other diverge.

In many cases, users of all-stainless equipment underestimate the advantages of single-use and overestimate the challenges. For example, only 35% of all-stainless users (and 31% of those using hybrid systems-systems that combine stainless and single-use components) perceive a cost advantage to all-disposable systems as opposed to 54% of those who actually use all-disposable systems. In another example: only 18% of respondents who use all-stainless equipment think that process reproducibility is an advantage to all-disposable equipment. In contrast, 31% who use all-disposable cite reproducibility as an advantage. Users of all-stainless may also overestimate challenges to all-disposable manufacturing lines. Twenty percent of respondents who use all-stainless equipment think that all-disposable equipment increases the risks of contamination. No one—0%—of those who actually use all-disposable equipment does.

The survey cannot determine how firmly held are these beliefs or what it would take to dispel them. But it's an interesting object lesson to me and perhaps to others who see science and scientists as purely objective.

I had another reason to consider attitudes toward disposables in particular. During the INTERPHEX 2011 conference, I hosted a panel discussion around continuous manufacturing. The discussion focused on traditional small-molecule, solid dosage forms. I learned that one of the hurdles is finding an automated method for moving powders from one unit operation to another—the answer to which for some products may be to keep all the chemistry in solution. It then occurred to me that a completely soluble process would start to look a lot like the process for biopharmaceuticals and could therefore benefit from the use of disposable components. If that's the case, then the "objective truths" of a whole new group of process developers and engineers will have to be overcome.I wonder how our survey results will look then. **PT**


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IBM Reboots Drug Discovery

Erik Greb

Can the semiconductor industry show Big Pharma how to develop innovative therapies?

Despite the adoption of new research strategies, the pharmaceutical industry's pipelines are slow to grow. Perhaps other industries will take up the challenge of developing new drugs.

It's already happening at IBM, where researchers have unveiled a biodegradable nanoparticle that targets and destroys antibiotic-resistant bacteria, such as *Staphylococcus aureus*. The nanoparticle's specific electrical charge draws it to an opposite charge on the surface of the bacteria. When it finds its target, the nanoparticle pokes holes in the bacterial membrane and empties out the bacteria, IBM researcher James Hedrick told *The Wall Street Journal*. By destroying the bacteria, the nanoparticle may prevent them from developing resistance.

The semiconductor industry has embraced many techniques (e.g., outsourcing, supply-chain management, and robotic technology) that drugmakers eventually adopted for their own purposes. IBM's development strikes me as another example of synergies that can be gained across seemingly disparate industries.

Finding the next blockbuster may be much more difficult now than it was in the past. But even if drug candidates are fewer, IBM's nanoparticle shows that technological innovations are increasing. If small- and large-molecule firms keep their minds and eyes open, they might come up with exciting new modes of action or methods of drug delivery. Maybe current challenges—and good examples—will stimulate drugmakers' ingenuity. **PT**

Erik Greb is an assistant editor of *Pharmaceutical Technology*.
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In the Field

Report from: Hungary

Sean Milmo

Eastern Europe's pharmaceutical leader—Hungary—is working to maintain its number-one status while also pursuing new avenues, especially in biopharmaceuticals.

Analysts have recently downgraded the short- to medium-term outlook of the $3.5-billion pharmaceuticals market in Hungary because of slow domestic economic growth, high unemployment, and, above all, government plans for a 30% cut in state-subsidized drug reimbursements. Prospects for the country as a center for pharmaceutical research and production, however, remain bright. *contin. on page 18*

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As Eastern Europe's most advanced pharmaceuticals industry, the Hungarian market has been able to take advantage of relatively high economic growth rates and a strong demand for medicines throughout most of the region, particularly in Russia, which is enjoying the benefits of high oil prices. Hungary began manufacturing drugs more than 100 years ago, and by the time World War II began, the country had created a large drug-manufacturing capacity. During 40 years of Communist rule, leading up to the late 1980s, the country formed a nucleus of pharmaceutical production for the entire Comecon trade bloc in Eastern Europe. (Comecon stood for the Council for Mutual Economic Assistance and existed from 1949 to 1991.)

Hungary's infrastructure and science base has since attracted multinational drug manufacturers, which have been investing heavily in the expansion of the country's production facilities, particularly in the areas of active pharmaceutical ingredients (APIs) and generic drugs. Among the global players with production facilities in the country are Roche, AstraZeneca, GlaxoSmithKline, Pfizer, Teva, and Novartis.

Around 75% of the turnover of the industry stems from exports, much of it from generic products. In 2010, total pharmaceutical exports amounted to €2.9 billion ($4.2 billion), that's a 250% increase from 2005. During the same five-year period, imports rose 188% percent to €2.6 billion ($3.7 billion).

Today, the sector is shifting more toward biopharmaceuticals and other higher value products, particularly follow-on biologics. The strategic change, and resulting innovative products, should help Hungary to be less reliant on Eastern European sales by enabling it to make inroads into the wealthier Western European market.

Gedeon Richter, which is by far the largest Hungarian-owned pharmaceuticals company and the biggest domestically-owned drug manufacturer in Eastern Europe, has been setting the pace for the sector overall. The company has made acquisitions in Switzerland and Germany, with a focus on gynecology products and oral contraceptives.

Gideon Richter is also building a follow-on biologics plant in Debrecen in eastern Hungary with the aim of marketing biosimilars in Europe in two years. In late 2010, the company entered into a collaboration agreement with Mochida of Japan on the development and marketing of Richter's follow-on biologics in Japan.

Approximately 90% of Richter's €992 million ($1.4 billion) sales in 2010 came from abroad, mainly from Russia (22%), Poland, and Romania. The company's approach for remaining competitive in the long term is to maintain a portfolio of high-added value products.

"We are able to adopt this new strategy because we have the freedom of being an independent company without being owned by an international pharmaceutical company," says Zouzsa Beke, Richter's communications director. "We are also doing it without the backing of a strong government industrial policy like that in other EU countries. There are R&D incentives from the government but they are not significant, and capital allowances only apply to large investments."

Some of the Hungarian subsidiaries of international companies, such as Egis, which is majority-owned by Servier of France, are also planning to enter the follow-on biologics sector, although not necessarily as producers initially.

Hungary's National Economy Minister Gyorgy Matolcsy stated last month that the government wants the country to be one of the top 10 leading biotechnology centers in the European Union by 2020–2025.

However, small biopharmaceutical companies, which make up most of the fledgling biotech sector outside the multinational firms, complain about lack of funds from Hungarian financiers.

"The few venture capitalists are not interested in biotechnology because they don't understand it, and the banks are even more reluctant to invest in what they see as high risk innovations," explains Zsolt Lisziewicz, chief operating officer of Genetic Immunity, Budapest, a biopharmaceuticals start-up in nanomedicine immunotherapies. "We would like to build a plant in Hungary once we have a commercial product, but we may have to do a NASDAQ floatation to get the funds."

Hungary, which is outside the euro zone, is still gripped by a credit squeeze after having to be rescued by the International Monetary Fund (IMF) four years ago. With easier access to funds, its pharmaceuticals sector might be performing even better in the European markets.

Sean Milmo is a freelance writer based in Essex, UK.

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 May issue (available at www.PharmTech.com/PTSM):

- Chan Harjivan and James Guyton with PRTM analyze biopharmaceutical distribution and administration in public, government, and developing-world markets
- Report on the green manufacturing and sustainability partnership between GlaxoSmithKline and the Singapore Economic Development Board
- A roundup of CSR and sustainability news.

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Global Healthcare on the Ground

Roche Takes on Illnesses in LDCs

Christina I. Ortiz

Pharmaceutical global health initiatives play a big role in educating health workers in least developed countries (LDCs) by providing the skills and tools necessary to develop life-saving drugs and to limit the spread of disease. Roche is just one pharmaceutical company involved in such efforts around the world. The company's collaborations and partnerships with government and other healthcare providers, as well as their own initiatives, have influenced health movements that are benefiting local communities globally.

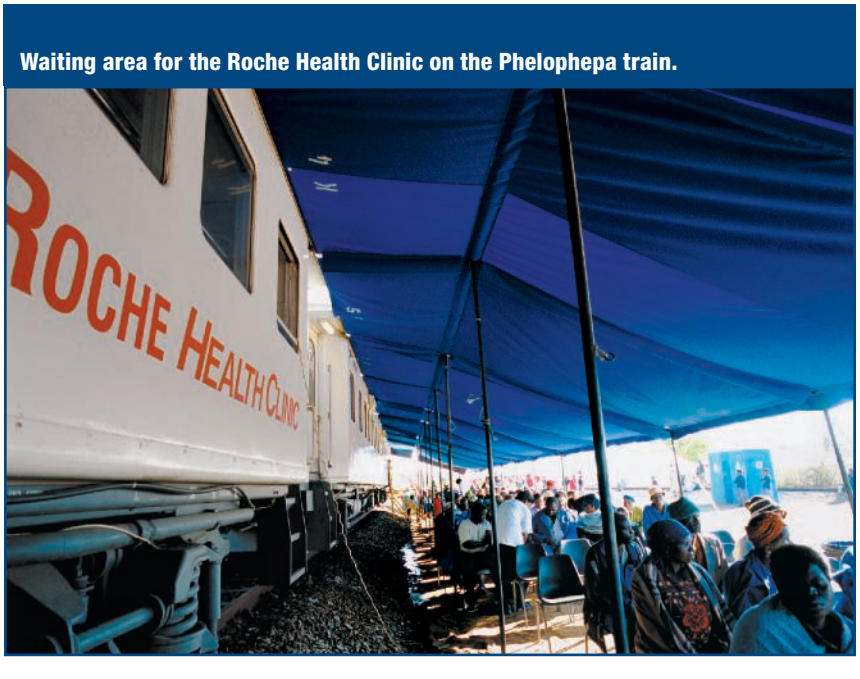
The EDUCARE (EDUcation for Cancer in African Regions) project is a partnership that began in April 2010, between Roche and the International Atomic Energy Agency (IAEA) to address the shortage of trained healthcare professionals in the oncology field in Africa. The program is governed and managed by a committee of representatives from Roche, IAEA, and the World Health Organization (WHO). The committee's main priority is to establish a Regional African Cancer Training network (RACT). The network would link cancer centers within sub-Saharan Africa to strengthen the transfer of knowledge to a broader group of healthcare workers. The project will also focus on the use of IAEA's Virtual University for Cancer Control (VUCC), which will serve as an online university and mentoring community across Africa. Roche and IAEA have committed to a five-year pilot of VUCC in Ghana, Tanzania, Uganda, and Zambia.

In 2006, Roche committed to an AIDS Technology Transfer Initiative to provide companies in LDCs and sub-Saharan Africa with free, on-site technical help to manufacture generic versions of the company's drug Invirase, a second- line protease inhibitor that hinders viral replication of HIV-1 and HIV-2. Developing countries face an increasing need for second-line treatments and, with the training and knowledge exchanged provided by Roche, companies in LDCs are now able to produce these drugs locally. In 2008, Roche expanded this initiative with a series of pan-African training seminars for local manufacturers. Attendees learned how to better comply with cGMPs in their therapeutic areas.

In July 2009, Roche announced the Tamiflu Reserves Program (TRP) for developing countries. The program ensures that, should WHO declare an influenza pandemic, Tamiflu will be readily available to governments and patients in developing nations. Under the program, Roche produces and stores Tamiflu stockpiles for developing countries at a reduced cost. Qualifying countries for the program include most members of the Global Alliance for Vaccines and Immunizations.

The partnership programs that Roche participate in, such as those highlighted here, focus heavily on education for medical and scientific professionals and patients as well making healthcare more accessible to those who cannot obtain it, either because of financial or geographical challenges.

According to Roche spokesperson Claudia Schmitt, the company's approach to working in partnerships is "to find the most feasible ways of removing barriers within the ethical, legal, regulatory and commercial constraints that determine the delivery of healthcare in that country." She adds that this approach has "established a transparent policy for all our medicines so intellectual property is not a barrier to any of our medicines in the world's Least Developed Countries."



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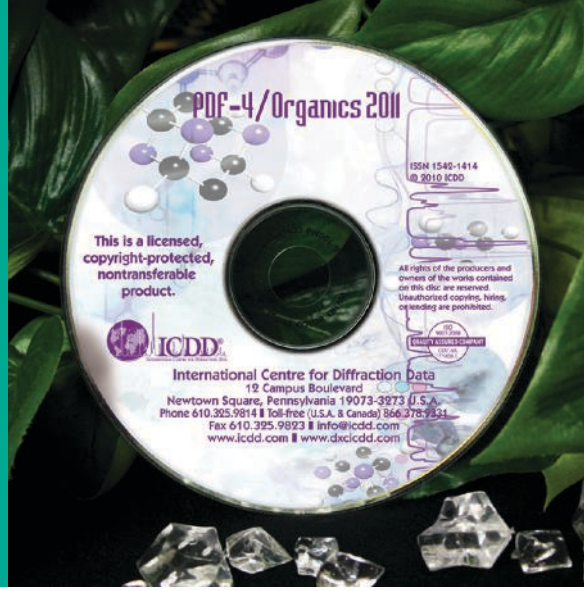

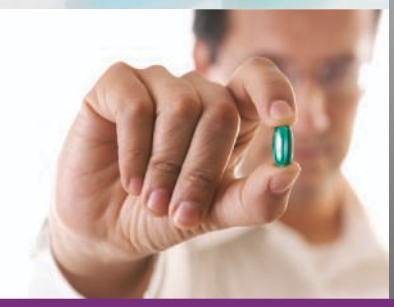

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Zone in on: Manufacturing

J&J Reorganizes Consumer Group

Erik Greb

On Apr. 4, 2011, Johnson & Johnson (J&J) instituted a new structure for its Consumer Group. The group now includes a Global Franchise Organization that consists of four consumer categories: skin care for babies and adults, over-the-counter (OTC) medicines, oral care and topical health, and women's and intimate health, according to a *Reuters* report. Research and development will be among the Global Franchise Organization's activities.

The company created four regional divisions: North America, Asia–Pacific and Europe, the Middle East, and Africa and Latin America. The divisions will market J&J's various consumer product lines, with the exception of the North America region. The latter division will market all product lines except OTC medicines sold in the United States. A new US OTC business headed by Pat Mutchler will market those products, according to *Reuters*. In addition, Marc Robinson, head of J&J's consumer-healthcare businesses, and Peter Luther, president of McNeil, will be given new assignments, according to Reuters.

J&J told employees of the organizational changes in an internal company memo in February 2011, according to Reuters. In the memo, the company said that the regional and franchise structure would enable quick reactions to changing market conditions and the efficient execution of regionwide initiatives, while accelerating growth in emerging markets, according to *Reuters*.

On Mar. 10, 2011, FDA filed a consent decree against McNeil, a subsidiary of J&J, for failing to comply with current good manufacturing practice requirements. The agency prevents McNeil from manufacturing and distributing drugs from its Fort Washington, Pennsylvania, facility until FDA determines that its operations comply with the law. The facility manufactured OTC products, including children's Tylenol, Motrin, Zyrtec, and Benadryl products.

In addition, the decree requires McNeil to destroy all drugs that have been recalled from the Fort Washington; Las Piedras, Puerto Rico; and Lancaster, Pennsylvania; facilities since December 2009. McNeil must retain an independent expert to inspect the facilities and evaluate whether the violations have been corrected.

»PharmTech Poll

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Zone in on: Regulation

Congress Overhauling US Patent Laws

Amy Ritter

The US patent laws are undergoing a major revision, the first large revision since the Patent Act of 1952. The America Invents Act, introduced by Senator Leahy (D-VT) on Jan. 25, 2011, was overwhelmingly passed by the US Senate on Mar. 8, 2011. It was then introduced to the House of Representatives on Mar. 30, 2011. On Apr. 14, 2011, the House Judiciary Committee met and voted on amendments to the act. The bill will soon move to the House floor for a vote.

The act introduces reforms that bring US patent law more in line with those of the EU. In particular, it revises policy such that patents will be granted on a first-to-file basis, rather than first-to-invent. Under the old system, if there was a dispute about who was first-to-invent, it was settled by a division of the US Patent and Trademark Office, an expensive and uncertain process that put cash-strapped academics at a disadvantage.

First-to-file is a much less ambiguous measure of who has first claim on an invention. This system carries some risk to academics, particularly if they begin the process of commercialization before filing. However, the act contains provisions intended to safeguard inventors, such as the ability to request a post-grant review during the first nine months after issue, and a provision allowing third parties to submit prior art during patent examination. First-to-file status is intended to remove much of the ambiguity around patent filings, and enable a more streamlined, less expensive patent application process.

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Do it my way

"We hired the former senior vice-president of quality for a top-10 pharma company as a consultant," explained our GMP Agent-In-Place. "He demanded that we do things the way he had in his former position, including those actions that were required of him by a single Mid-Atlantic region national inspection expert. His procedures included having the vice-president review and sign every deviation in the company. Later on in his consulting period, he had the gall to note that we shouldn't react to the preferences of a single inspector."

Iced water

"You wouldn't think cold weather would hurt a freeze-dried product," began our GMP Agent-In-Place. "But when we heard that our broker left our freeze-dried product out on the tarmac upon receipt at a Canadian airport, we knew we were in trouble. The product is packaged with sterile-water diluent, and if the diluent freezes, it can break the diluent vial or create a microsized crack that can provide an entry point for contamination. Either way, the product was no longer unusable."

Cad

"One of our injectable products had an unusual peak in a laboratory release test result," recalls our GMP Agent-In-Place. "Further analysis showed minute quantities of cadmium. We couldn't imagine where the cadmium was coming from, but we checked all the production materials that had been used.

"This particular injectable product underwent some filtration processes during purification that were assisted by the use of filter aid. Filter aid is a mined material (i.e., it comes right out of the ground)," explained our Agent. "It varies in quality as a result, and apparently one area that was mined has some cadmium contamination by unknown processes. We now have a more intensive test process for the incoming raw material."

Reaching the LIMit

"What a mess," groused our GMP Agent-In-Place. "We were retiring two older laboratory information management systems (LIMS) and replacing them with a global LIMS system for use at two sites. Unfortunately, our business requirements document turned out to be site-specific. In the implemented LIMS system, functions that would work well for the process flow on one site were all wrong on another. So each site had some gaps in what worked. This was particularly bad for one site which had to hire additional personnel because the workarounds for the new LIMS required manual rather than automatic functions. While we plan on fixing some of the issues, it may be just throwing good money out the door."

Seeing red

"During final inspection of an injectable product, we found hundreds of bottles with red specks on the bottle necks," our GMP Agent-In-Place reported. "We opened a deviation investigation and started looking for the cause of the specks. Our first thought was stopper material, but this proved wrong because the specks were imbedded into the glass. Analysis showed the specks to be ferric oxide, better known as rust. This finding confused us because we perform a 100% inspection of the glass bottles before filling them. We sent the containers to the glass manufacturer to investigate the source of the specks. It turned out that the glass manufacturer had set up the bottle-molding machinery poorly, and there was some rubbing of the neck molds, resulting in scraping small flakes of steel off of the molds and onto the molten glass where it solidified into place. Our prefill inspection process didn't catch the silver bits of metal, and only after the glass bottles went through the bottle washer and the high-temperature, dry-heat sterilizing tunnel did the steel turn to rust and become easy to see." **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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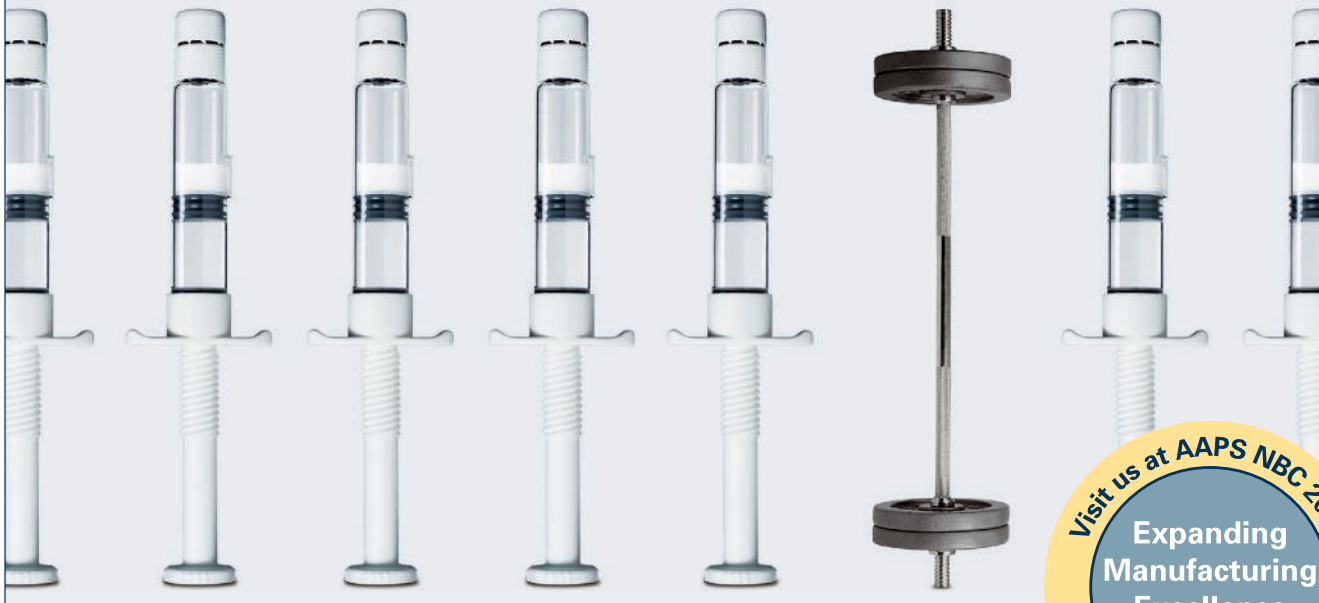

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Editors' Picks of Pharmaceutical Science & Technology Innovations

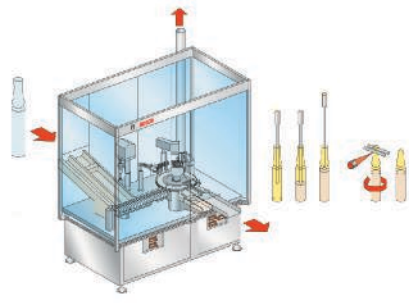
Consumers may think of a package as little more than a container bearing company and product names. Pharmaceutical firms, however, undestand that packaging can perform many functions (e.g., simplifying patient compliance or maintaining product temperature). This month's products help ensure that drug packaging fulfills manufacturers' requirements. Two self-contained machines from Bosch perform the whole filling and closing process for ampuls and vials. An instrument from PTI Inspection Systems checks for defects in packaging that might be difficult to spot. Prefilled syringes from Globe Medical Tech help improve patient compliance.

Ampul-filling machine reduces particle generation

Bosch's ARF 1010 and ARF 1020 machines can process open and closed ampuls, or open ampuls in combination with vials. The units perform the entire filling and closing process—customers do not need a separate machine to overcap vials. The ARF 1010 unit has a one-position filling station, and a version with a two-position filling station also is available.

Containers are suspended during transport in the starwheel. This design ensures that transport is gentle and protects vials from scratches and cosmetic damage. At the closing station, a special holder rotates injection vials for closing, rather than rotating the vials' caps. This feature, combined with the gentle transport, reduces particle generation.

The unit's digital flow meter is designed to ensure the reproduction of flame regulation for the closing of the ampuls. The flame is ignited automatically and can be activated easily from the machine's operator interface.



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Sensitive system detects leaks

The HVLD Micro Leak Detection System from PTI Inspection Systems and Nikka Densok USA provides a nondestructive means of detecting pinholes, cracks, and defective seals in pharmaceutical packaging. The device's electrode probes scan glass, plastic, and poly laminate containers that are filled at least 30% with liquid. Differences in current flow indicate breaches in the container. HVLD can be used on various liquid-based products, including suspensions, emulsions, and proteins. The offline laboratory unit helps personnel determine the approximate location of the breach.

Prefilled syringes enhance safety

Globe Medical Tech's dual- and single-chamber prefilled syringes are designed to enhance safety. The syringes' integrated needle-stick prevention feature and vacuum needle autoretraction technology provide full compliance with US and European safety regulations. After injection, the needle is retracted into the syringe body with a gentle push on the plunger. The syringe does not need any activation (e.g., twisting or capping) to engage the safety and contains no springs or metal components.

Prefilled syringes
Globe Medical Tech
www. safety.globemedtech.com

In combination with material and lubricant selections, the single- and dual-chamber syringes help maximize pharmaceutical compatibility. The dual-chamber syringe maintains the pharmaceutical components in separate chambers, thus extending the shelf life of some drugs. The syringes are made with medical-grade plastics that comply with FDA and international pharmacopoeial regulations. The plastics are compatible with a wide range of pharmaceutical drugs, and the components offer biocompatibility and low leachability. The syringes are designed to reduce dosing errors and contamination.

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Experts Ponder Ways to Fill Pharma Pipeline

Jill Wechsler

FDA, NIH, and industry seek new strategies to spur drug development and promote access to therapies.

Drug-development pipelines have shrunk; fewer new products are being approved for market; and the prospect of significant declines in revenues due to the looming "patent cliff" is prompting pharmaceutical companies to scale back research and development (R&D). Pfizer rocked the industry in February by announcing a major cutback in R&D spending, including plans to shutter its long-time research facility in Sandwich, United Kingdom, and to reduce its Groton, Connecticut, research facility. As part of a move to cut its $9-billion R&D budget to some $6-7 billion by 2012, Pfizer is moving antibacterial research from Groton to Shanghai, China, and will use its Cambridge, Massachusetts, research operation to form more links with small biotechnology firms in the area.

The crisis in the pharmaceutical industry is generating a serious search for new business models. Manufacturers are looking to partner more with small biotechnology firms and academic research institutes, to shift research and production operations overseas, and to streamline operations and reduce waste wherever possible. The National Institutes of Health (NIH) proposes to ramp up support for translational medicine that will shepherd basic research through the R&D "valley of death" to yield new therapies. Patient advocacy groups are consulting with and providing funding for public and private therapy development programs. America's position as the world leader in biomedical R&D is "under siege today," and facing its biggest threat in 65 years, commented former Congressman John Porter, at a forum in March 2011, sponsored by ResearchAmerica. "Is America going to put progress on hold?" he asked in calling for decision-makers to consider the importance of science and innovation in making spending decisions. These trends are shaping many aspects of biopharmaceutical development, production, and marketing.

The crisis in the industry is generating a serious search for new business models.

Slowdown at FDA

Some of the blame for longer, more costly drug development falls on the shoulders of FDA. Stepped-up demand for more safety and efficacy data, prior to approval as well as after a drug comes to market, can add to development costs, and ultimately weaken less robust pharmaceutical R&D programs. Moreover, success rates remain notably low for new drugs in clinical development, despite years of efforts to better inform the clinical-research process to avoid wasting millions of dollars on unsuccessful studies. The Biotechnology Industry Organization (BIO) reported in February that only one in ten new drugs make it from Phase I studies to FDA approval, based on an analysis of thousands of drug-development efforts from 2003 through 2010.

Most disappointing is an actual decline in new drug approvals by FDA last year, a troubling shift after two years of slight increases. The agency cleared only 21 new molecular entities (NMEs) in 2010, down from 25 in 2009. Even more discouraging are reports that fewer applications for innovative new therapies were filed with FDA last year, squelching optimism about an upturn in product approvals in the near future. Yet, FDA is caught in a hard place, as patient advocates demand earlier access to promising

Jill Wechsler
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In Washington this month

- FDA drug approvals have declined, along with the number of new applications.
- After struggling to implement FDAAA, FDA is establishing a a quality management system for a more efficient application-review process.
- NIH is promoting translational medicine as a way to boost new drug development.

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A recent New England Journal of Medicine study highlights how public-sector support for applied research has led to dozens of new FDA-approved medicines, challenging the assumption that all new drugs come from pharmaceutical industry research and development (1). The aim is to show that publicly supported research institutions, including universities, research hospitals, and federal laboratories, play a key role in drug discovery, as opposed to basic research into underlying mechanisms of disease.

The study shows that about 9% of all new drugs approved by FDA between 1990 and 2007 came from publicly supported organizations, and more than 20% of new drugs qualifying for priority review. Such data may encourage more public–private collaboration, as all parties seek to capitalize on all available skills to improve drug-development success rates.

Source

1. A. Stevens et al., NEJM 364.6, Feb. 10, 2011.

therapies, while policymakers and consumer groups insist on more scrutiny of test products to better detect potential safety problems.

The approval downturn kept several highly touted experimental products from the market. Cardiovascular safety issues prompted FDA to reject new diabetes therapies and kill several new weight-loss drugs, while also pulling Abbott's Meridia product from the market. More recently, a promising fast-acting inhaled insulin product (MannKind's Afrezza) was put on hold following FDA requests for more data on product usage and safety. The agency drew heat for turning down an application from Cell Therapeutics for pixantrone, a treatment for non-Hodgkin's lymphoma that showed some efficacy, but not enough for FDA approval. Cancer advocates continue to oppose a move by FDA to narrow its approved indication for Avastin, insisting that the benefits outweigh new evidence of serious side effects.

There are some bright spots amidst these disappointments. Last month, FDA approved a new treatment for melanoma, Bristol-Myers Squibb's (BMS) Yervoy (ipilimumab). The drug is the first to prolong lives of patients with this deadly skin cancer and a vast improvement over existing therapies. Even better for the manufacturer is an expectation that this new monoclonal antibody, which enlists the body's immune system to attack cancer cells, could lead to similar treatments for other cancers.

FDA also made headlines earlier this year by approving the first new treatment for lupus in more than 50 years—Benlysta (belimumab), developed by Human Genome Sciences with support from GlaxoSmithKline. The drug's discovery relied on information resulting from human genome mapping and represents the first real success in this field after multiple failures.

BMS cites its new cancer drug as evidence that an increased focus on pharma R&D can yield big dividends. "R&D pays," stated CEO Lamberto Andreotti in an interview with the *Wall Street Journal*, noting that the firm is investing research money very carefully in a range of disease classes and expects to have four more new therapies approved by FDA in another year. Merck similarly told Wall Street analysts in February that it's not cutting back on its $8 billion R&D spending plans, even though the decision may result in missing long-term profit forecasts.

Last year's slim drug-approval list included several notable products. Amgen won approval for osteoporosis treatment Prolia (denosumab), and Roche's Genentech brought out Actemra (tocilzumab), an intravenous drug for rheumatoid arthritis. Boehringer Ingelheim won the race to bring to market a new blood-thinner Pradaxa (dabigatron), although others may catch up soon. Probably the most exciting new product was Dendreon's therapeutic prostate cancer vaccine Provenge (sipuleucel-T). Other new vaccines for meningococcal disease and pneumococcal disease also were approved by the Center for Biologics Evaluation and Research (CBER).

Seeking improvement

FDA officials say that drug approvals are returning to former on-time schedules after sagging in recent years as the agency struggled to implement a host of new requirements established by the FDA Amendments Act (FDAAA) of 2007. Last year, the Center for Drug Evaluation and Research (CDER) began to benefit from staffing increases and regulatory clarification, which helped employees achieve review timeframes more steadily. Now the agency is moving into a "period of consolidation," says CDER Director Janet Woodcock, as it completes multiple FDAAA initiatives, negotiates a new Prescription Drug User Fee (PDUFA) program, and establishes a quality-management system for more efficient 21st century review process.

Woodcock reported in December 2010, at an FDA/CMS summit, that the agency once again was meeting user fee timeframes for processing applications, particularly submissions for NMEs, and that the "big wave in missing goals is coming down." There also are more first-cycle approvals, a key benchmark for both sponsors and regulators, and the rate of first launches in the US is holding steady.

At the same time, FDA is looking to improve the regulatory process in ways that encourage new product development. Combination therapies, for example, stand to benefit from draft guidance issued last December on codevelopment of investigational drugs used in combination, which is particularly germane to formulating new cancer therapies.

The looming reauthorization of PDUFA in 2012 is prompting a re-evaluation of the agency's Risk Evaluation and Mitigation Strategies (REMS) program to meet industry concerns about too many diverse REMS formats; lead proposals are to have less burdensome controls for REMS that only require distribution of medication guides, and to devise common formats for such documents. FDA recognizes, says Woodcock, that REMS requirements should not delay product approvals.

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FDA-industry user-fee negotiations also seek to make presubmission meetings more productive and to support new strategies for streamlining product testing and application review. Discussions regarding generic-drug user fees, moreover, are moving forward. A main objective for FDA is to gain additional support for more timely plant inspections in the face of a notable rise in foreign sourcing of active ingredients as well as generic-drug production.

Another area of focus is FDA's accelerated-approval process, which is designed to avoid delays in moving important new therapies to market. The system has been criticized because manufacturers often fail to complete agreed-on confirmatory trials in a timely manner, and some follow-up studies have shown limited efficacy and serious side effects, as with Roche's Avastin. FDA officials have proposed that sponsors launch confirmatory trials before the agency grants fast-track approval to ensure that additional studies are performed according to plan.

Great difficulties in developing new drugs for broad patient populations, such as diabetics and the obese, are prompting collaborative efforts to better understand approval requirements. Woodcock and her staff recently met with a group of obesity experts to discuss standards for bringing weight-loss drugs to market. The scientists proposed that regulators consider the broader health benefits of weight loss, such as reduction in sleep apnea, in assessing potential side effects from drug therapy.

FDA Commissioner Margaret Hamburg continues to stress the importance of advancing regulatory science in order for FDA to be able to support the translation of science into real-world therapies. New biomarkers for toxicology can identify drugs likely to fail much earlier in the process and also better target therapies to individuals most likely to respond, Hamburg noted.

Also, innovative clinical-trial designs can yield answers using fewer patients and less money. The conventional thinking is that new discoveries from biomedical research will lead to new products. But, she explained at the ResearchAmerica forum, there is a regulatory science gap that can prevent new opportunities from coming to fruition.

Promoting translation

The changing biomedical research landscape and cutbacks in industry R&D programs are encouraging more public support for pharmaceutical research around the world. The Innovative Medicines Initiative in Europe is building a schizophrenia database of industry-sponsored clinical trials to better identify signals of patient response to test drugs. The United Kingdom's Medical Research Council has established the Developmental Pathway Funding Scheme to support basic research on drugs and medical devices, and the Wellcome Trust's Seeding Drug Discovery initiative is funding efforts to take drug candidates through early clinical trials. Both US and EU scientists are wary of being left behind by soaring Chinese investment in R&D.

At home, NIH director Francis Collins has launched a high-profile campaign to promote translational medicine as a way to spur development of new medical treatments that can benefit patients. In December, an NIH advisory committee recommended establishing a new NIH National Center for Advancing Translational Sciences (NCATS), a move engineered by Collins to bring together a number of NIH programs that provide resources for translating basic discoveries into new medicines and diagnostics. These include a program that supports development of therapies for rare and neglected diseases, along with NIH's national network of research sites at academic medical centers supported by Clinical and Translational Science Awards.

As the former director of NIH's Human Genome Project, Collins is optimistic that new genetic discoveries can chart pathways for discovering new medical treatments, and that the emergence of more well-validated genes will be useful in "identifying drug targets

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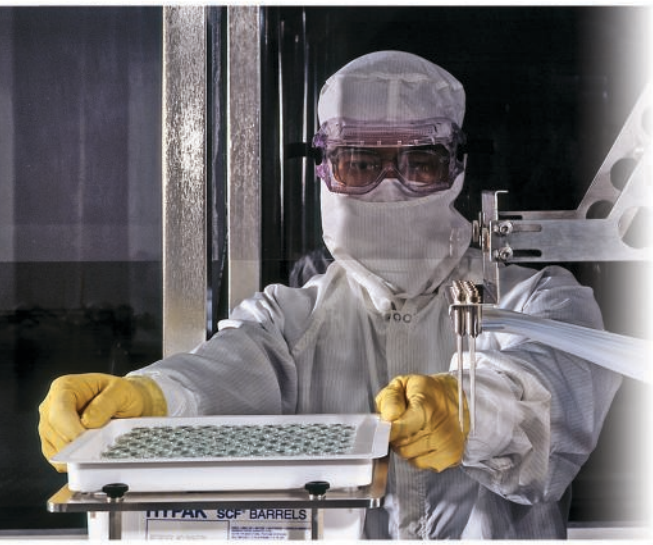

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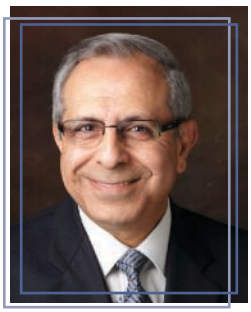

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in unprecedented numbers," he said in an interview. The scientific enterprise is yielding up a lot of new ideas about therapeutics, he observed, yet "traditional private sector efforts to capitalize on that are taking a hammering." NCATS aims to bolster the funding of research projects at a time when biotech and pharma companies face serious financial challenges.

Along these lines, the initiative also will encourage more collaboration between academic researchers and biopharmaceutical companies and to strengthen ties with FDA to ensure that NIH-sponsored studies provide the data needed to support registration of new products.

The project envisioned by Collins will help re-engineer the drug-development pipeline by investing in new assays that can screen thousands of molecules to find ones that will hit defined disease targets. Another objective is to improve assessment of toxicity, which may involve shifting from the use of animal testing to identify potential problems.

As part of the process, Collins' translational science campaign aims to convince Congress and the American public that the federal investment in biomedical research can pay off in terms of new, life-saving therapies (see sidebar, "Public funds yield more medicines"). The Obama administration has proposed a very slight increase in the NIH budget for fiscal year 2012, which would just barely maintain current funding levels. Even during the Republican budget cutting campaign of the mid-1990s, NIH retained several strong GOP advocates on Capitol Hill and largely escaped the chopping block; that kind of support seems to be lacking among current Republican leaders.

Collins believes that today there is greater private sector interest in NIH-funded preclinical and clinical testing, as well as in compound rescuing or "repurposing." Pharmaceutical companies have long lists of compounds that have been abandoned along the way, maybe because a business plan changed or the money ran out or clinical trials failed to show efficacy, Collins notes. "We have been talking with leaders in the pharmaceutical industry about an opportunity to open the freezers and make such compounds available, with appropriate intellectual property protection for them," Collins explains. "This isn't a giveaway, but could be a win-win if such a compound were found to be active for a different application than originally considered." NIH will not move into drug development *per se*, Collins emphasizes, but will hand promising compounds off to private sector sponsors. **PT**

WEB: Read more of Jill Wechsler's columns at PharmTech.com.

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Manufacturing Strategies for Biosimilars

Albert Lee, Dinkar Saran, and Mark Mynhier

Innovator- and generic-drug companies need to adapt to compete in the biosimilars market.

Generic-drug manufacturers historically have replaced high-cost small-molecule drugs with low-cost equivalents by establishing relatively low-technology facilities and taking advantage of lower raw-material and labor costs. Today, a new set of patents is expiring, except this time it is innovator biopharmaceutical companies that stand to lose profits. Will history repeat itself?

Not if innovator biopharmaceutical manufacturers have something to say. Having invented the biopharmaceutical processes for some of the most expensive drugs, they must learn to adopt lean development and manufacturing practices to lower their cost of goods sold and achieve favorable gross margins.

Innovator companies are going head-to-head with generic-drug companies, of which some generate enough revenue to rank among the top 20 global drug companies. These generic-drug powerhouses have the working capital to invest in biosimilars. Such investment requires adapting a low-cost business model to account for completely different manufacturing processes, equipment, and employee skill sets.

The number of bioequivalence studies needed to ensure public safety and the resulting cost structure is one factor influencing the ability of the industry to provide low-cost biosimilars. These factors aside, looking at the development and manufacturing sides only, for biopharmaceutical innovators to be successful producing low-cost biosimilars, their focus must shift from innovation to replication. That change means developing strategies to transform expensive development and manufacturing processes into lean analogs.

Who can best meet the challenge of low-cost biosimilars?

To meet growing demand for biosimilars, innovators have to reduce the cost per unit dose and make the same amount of drug with fewer batches through higher fermentation titers, higher purification recoveries, and longer shelf-life formulations. Technologies, such as process analytical technology (PAT) enhance process predictability and understanding, thus minimizing batch rejections and increasing manufacturing run rates to produce batches more efficiently. Other technologies, such as disposable single-use systems (e.g., bioreactors, media and buffer tanks, and drug-substance container/closure systems) are effective, scalable, and inexpensive. Such technologies lower production costs by reducing the number of product-to-product and batch-to-batch changeovers and capital investments.

Novel drug-delivery technologies should be another area of focus for innovator biopharmaceutical companies. By enhancing the customer experience, these technologies could help boost market share and provide a source of sustainable competitive differentiation.

Generic-drug companies have to overcome a different set of challenges. Although these companies are adept at rapid development and low-cost manufacturing, biologics are more complex. Generic-drug companies will need the expertise to reverse-engineer the biologic and to develop a stable, therapeutically active cell line. They also will need to develop the manufacturing processes to meet specifications predictably and consistently while applying specialized analytical tools.

Additionally, investment in new infrastructure will be crucial for controlling living cells and for purifying biologics to produce biosimilars at commercial scale consistently. Companies must invest capital in bioreactors, purification suites, fill–finish operations, sterile environmental controls, and systems that are more liquids-based than solids-based.

To ensure stability during production, storage, and shipping, generic-drug companies must be able to characterize and mitigate the risk of degradation mechanisms of complex biologics. They also must, however, avoid long development times to maintain the revenue and market-share advantages that first-to-file status provides. Equivalency standards also may need to be scrutinized more closely because even small differences from the innovator drug (e.g. binding, activity, posttranslational modification, impurity profiles, and stability) can affect bioequivalence and put regulatory approval at risk.

Demand for lower-cost drugs, including biosimilars by governments, payors, and consumers is evident. The question is whether innovator or generic-drug manufacturers will be able to address the biosimilar business-model challenges to achieve a favorable outcome. **PT**

Albert Lee (alee@prtm.com) is an associate, **Dinkar Saran** (dsaran@prtm.com) is a principal, and **Mark Mynhier** (mmynhier@prtm.com) is a partner, all in the healthcare practice of the management consulting firm PRTM.

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INTERPHEX Innovations

Hallie Forcinio

Visitors found new container options, child-resistant concepts, and serialization solutions.

This year's INTERPHEX show presented a wide range of packaging innovations. Many machines offered enhanced flexibility, modular design, and compatibility with single-use product paths.

Modular design enables a high-speed aseptic filling and stoppering machine to operate in intermittent or continuous motion and to accommodate various filling methods, including powder filling. It's also easy to add as many as 12 filling stations or quality-control points, such as checkweighing. Fill volumes range from 0.25 to 100 mL. The servo-controlled machine operates at 400 vials/min with 100% checkweighing, and 600 vials/min if only a sampling of containers is checkweighed (Xtrema F2000 filling and stoppering machine, IMA Life).

Another highly flexible line can be aseptic or nonaseptic, handles glass or plastic bottles or vials, and can accommodate different filling systems with as many as eight filling heads. Three closing stations can be set up to handle various fittings, stoppers, and cap styles. The system also can incorporate pre- and postfilling gas flushing, empty- and full-container checkweighing with feedback loop, 100% torque measurement, inspection cameras, and labeling. On its maximum fill of 1100 mL, output can reach 120 bottles/min. Changeover takes 15 min (Kugler Linoline, Optima Group).

A blow-fill-seal machine designed for parenteral products eliminates hydraulics and the potential for oil leaks, related particulate generation, and cleanup issues. The 21 *CFR* Part 11-compliant equipment fills volumes from 0.2 to 500 mL and may be built with an isolator system. Container molds include from six to 30 cavities for outputs as high as 150 containers/min. Resin choices include low-density polyethylene, high-density polyethylene, and polypropylene. An optional ultrasonic cutoff system also helps minimize particulate generation (628 Asep-Tech blow-fill-seal packaging system, Weiler Engineering).

Ionized hydrogen peroxide (H_2O_2) sterilizes cleanrooms and isolator interiors 50% faster than traditional spray systems. With a concentration of 7.5% versus the traditional 35%, the ionized H_2O_2 quickly fogs the interior of the room or enclosure; can be removed faster; and kills bacteria, viruses, mold, fungi, and spores on contact, thus achieving a six-log reduction in microorganisms. It's also less corrosive and doesn't rely on humidity to work. In operation, the H_2O_2 is aerosolized with house air or a compressor system and passes through a 17,000-volt electric arc to quickly fog spaces as large as 1500 ft^3 (iHP 100 Mini Pod System, SixLog).

A washer for parenteral products cleans vial exteriors from the shoulder down to remove toxic product residue or improve label adhesion. The system replaces traditional vial-handling starwheels with parallel belts. Silicone cups along the bottom edge of the belts grip the vials by the cap and create a watertight seal that accommodates a high-pressure spray of water or detergent. Changeover between 13- and 20-mm vials requires no change parts. The washer contains only two moving parts and handles glass or plastic vials with volumes from 1 to 100 cm^3 at 200 vials/min (EVW-100 External Vial Washer, PennTech Machinery).

At the other end of the line, an aluminum capping machine has been redesigned to reduce particulate generation with direct-drive motors located in the base of the unit. The machine caps vial sizes from 1 to 100 cm^3, operates at 200 vials/min, and changes over in less than 10 min (AC-6 Capping Machine, PennTech Machinery).

A modular system helps optimize packaging operations for syringes, vials, cartridges, and eye-drop or nasal-spray bottles. Once the process is fine tuned at speeds as high as 10 units/min, it transfers seamlessly to higher-volume equipment. The choice of modules begins with filling options, including single-use, and may include

We'll be seeing more ...

- Servo controls
- Modular machines
- Single-use product paths
- Inserts with more panels
- CR packaging concepts
- Serialization.

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

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The Xtrema F2000 high-speed filling and stoppering machine from IMA Life has automatic feedback that adjusts the dose if fill volumes drift out of specifications.

checkweighing, stopper or dropper insertion, needle-shield assembly, sealing, crimping, and capping (DPS Development and Production System, Groninger USA).

Another product-development-oriented system applies silicone to the inside of syringe bodies to determine how much is needed to ensure that the plunger moves smoothly. The semiautomatic unit can be loaded with 35 syringes and treats as many as 10 containers/min. Since the benchtop system is based on the same technology as the production-scale machine, the transition from laboratory or pilot line to full-scale production is seamless (SVS 9061 Silicone Spraying Unit, Bausch and Stroebel Machine).

Another benchtop system, a microprocessor-controlled powder filler with two heads, fills doses ranging from 50 mg to 75 g with ±1% accuracy. The filling process eliminates scraper blades and features a dual-level supply hopper and agitator. In operation, vacuum draws the powder into the dosing chamber. When it is full, the vacuum cuts off, and a pinch valve opens to create a pathway to the filling head. Positive pressure moves the powder through the dosing head into the container. After the fill is complete, a high-pressure pulse cleans residue from the chamber and filter, and deposits it into the container, thus eliminating waste (PF2TT Powder Filler, Cozzoli Machine).

A servo-driven benchtop filler fills liquids semiautomatically or automatically. Four rotary piston pump sizes handle fill ranges of 50 µL to 1.5 mL, 1–10 mL, 5–30 mL, or 10–100 mL. Models include single-, dual-, and five-head configurations. Systems can be cart-based, integrated with an X–Y table, or mounted on a vial or syringe filling machine (FSR 1000 single-head, FSR 1002 dual-head, FSR 1005 five-head benchtop filler, Colanar).

For solid dosage forms, a high-speed tablet counter fills 100-count bottles at as many as 120 bottles/min. The electronic system includes 20 central processing units (one per channel), can be set up quickly, needs no tools for changeover, and tracks downtime.

With a built-in vacuum pump, Cozzoli's PF2TT powder filler needs only an air connection and 115-volt power supply.

The touch-panel interface on Colanar's benchtop filler stores as many as 50 recipes in its memory.

A prehopper removes broken or damaged tablets. Good product moves into the pressure-free main hopper, where it is accelerated so that it drops single file into the bottle. With an optional communications package, the machine can send alerts through email or Smartphone (Street Fighter 100 tablet counter, Capmatic).

Single-use systems

Because of growing interest, several exhibitors showcased single-use systems. A 50-cm^3 peristaltic pump for single-use dosing systems has joined a 6-cm^3 option. Tubing can be removed and replaced with one hand. Offset rollers minimize pulsation and improve fill accuracy to ±0.5 mL (PreVAS Single-use Dosing System, Bosch Packaging Technology).

At least four other firms offer peristaltic pumps for single-use systems (Bausch and Stroebel, Watson-Marlow, Flexicon Liquid Filling, and Colanar). But, peristaltic pumps are not the only style available for single-use systems. A single-use rolling-diaphragm pump built of polycarbonate with a platinum-cured silicone diaphragm is assembled in a cleanroom, 100% integrity tested, and delivered with custom tubing sets. The prevalidated, presterilized, and preassembled system offers accuracy of ±10 mg on fills equal to or less than

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2 mL and ±0.5% on fills greater than 2 mL (PreVAS Dosing System).

A disposable turning valve pump also is supplied as part of a preassembled, presterilized system, which includes tubing and filling needles. Targeted for vials, eye-drop bottles, syringes, and cartridges, it offers high accuracy on fills from 0.1 to 3 mL and handles virtually any liquid, including highly viscous or shear-sensitive ones (Disposable Filling System, Groninger).

New inkjet coders

For coding needs, a 35 character/s continuous inkjet (CIJ) printer is reportedly 20% faster than competing systems. The IP65-rated unit is washdown compatible and recirculates solvent so that it consumes only 2 mL/h, compared with 4–7 mL for other systems. With only six moving parts and a simplified ink system, maintenance requirements are minimal. The printer also features a removable operator interface and uses volatile organic compound-free inks (alphaJET evo continuous inkjet printer, Oncode).

Another CIJ printer needs no preventative maintenance at all—just routine replacement of consumables, which are color-coded for easy identification. A modular design eliminates the traditional ink reservoir and separates ink and filters from pump and associated electronics so that ink disposal doesn't scrap viable mechanical and electrical components. Other features include a simplified operator interface and range of input–output options to simplify integration with other equipment (A320i printer, Domino North America).

Inserts increase

As FDA requires more information in medication guides and patient information, the size of package leaflets and outserts is increasing. One of the biggest measures 630 in.^{2}, but folds into a 1.25 × 1.25-in. square with 210 panels, which is substantially more than the previous maximum of 170 panels (leaflet–outsert, Mini Graphics). Printed materials also may include 3-D graphics that rely on the same software used for 3-D imagery in video games and 3-D movies to create accurate color, texture, and size (3D Label Graphics, Mini Graphics).

It's possible to fold an insert to a size even smaller than 1.25 × 1.25 in. At 1.125-in.^{2}, the insert can be applied automatically and consist of approximately 200 panels (Glued Capsert, Arthur Press).

If one sheet isn't big enough, two or more inserts can be stacked together. One piggybacked concept compatible with automatic application features two 1.25-in.^{2} inserts with as many as 170 panels each (multiserts, Cortegra and Chesapeake Pharmaceutical and Healthcare Packaging; multipack bundles, The Challenge Printing). **PT**

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Re-examining Over-the-Counter Drugs

Angie Drakulich

There are more than 250,000 over-the-counter (OTC) products on the market today with wide access to consumers. But after a series of major OTC drug recalls, regulators and standard-setting bodies seem to be taking a closer look at these readily available products.

Although industry is familiar with the process by which over-the-counter (OTC) products reach the shelves, many consumers may not fully understand the difference between regulatory approvals for prescription products and the majority of nonprescription products. They may not know, for example, that FDA does not perform a prereview of chemistry, manufacturing, and controls (CMC), labeling, or pharmacokinetics for products regulated under the OTC Monograph System. Unlike prescription products, OTC drug products may or may not require clinical studies, and manufacturers of OTC monograph drugs are not required to pay user fees (1). The fact is, OTC drug products have their own rules, and they are approved in various ways depending on when they are (or were) developed and submitted to FDA for marketing approval.

OTC approvals: a brief history

Before the 1960s and 1970s, OTC drug sponsors were not required to demonstrate drug effectiveness. But in 1962, FDA required manufacturers to show effectiveness, and in 1972, the agency began what's known as the OTC Monograph System (also called the OTC Drug Review process), a project that is still underway today. The project involved reviewing in great detail the hundreds of compounds available to consumers in OTC form and developing FDA monograph requirements for drugs to be considered as generally recognized as safe and effective (GRAS/E).

All drugs, including OTCs, for human use in the US market must: adhere to current compendial standards; meet labeling requirements called for in the *Code of Federal Regulations (CFR)* and in the Federal Food, Drug, and Cosmetic Act; and be manufactured according to cGMPs, which are outlined in 21 *CFR* Parts 210, 211, and 330 (2). GMP compliance is verified through FDA inspections. Any OTC drug that deviates from a final monograph is not recognized as GRAS/E and requires an approved application (i.e., a new drug or abbreviated new drug application, NDA or ANDA) before it can be marketed (3). OTC drugs that meet final monograph requirements do not require an application approval.

Compendial drug quality monographs, or written standards, are published and maintained for the US marketplace by the US Pharmacopeial Convention (USP) and published in the *USP–NF*. FDA monographs, which are for conditions for market entry, are published in the *CFR*. An OTC drug monograph includes requirements for the active ingredient's dosage strength and form as well as for the product's labeling and final formulation testing (1).

As part of the OTC Drug Review process, FDA ended up restricting in the 1970s the use of some 500 active ingredients that had previously been on the market because of a lack of sufficient demonstration of effectiveness or lack of general recognition of safety. To date, the agency has completed a review of more than three-fourths of the original monographs proposed at the inception of the program, according to FDA spokesperson Lisa Kubaska. Certain OTC medicines can be reviewed again when a monograph is amended or when a new question of safety or efficacy is raised.

Since about 1984, most new OTC drug products have gone through the NDA/ANDA process for market approval, although companies can still submit applications to get into the monograph system. Figure 1 provides a full historical timeline of OTC drug regulation.

Despite the differences in OTC monograph-drug reviews, NDAs and ANDAs for nonprescription products are examined in the same manner as

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prescription products. According to FDA, there are 774 OTC products on the market today that were approved by NDA or ANDA.

Another mechanism by which a drug can enter the market as an OTC drug is to undergo a status switch from a prescription drug to a nonprescription drug. The labeling process for this type of switch is quite complex and described later in this article.

Monograph modifications

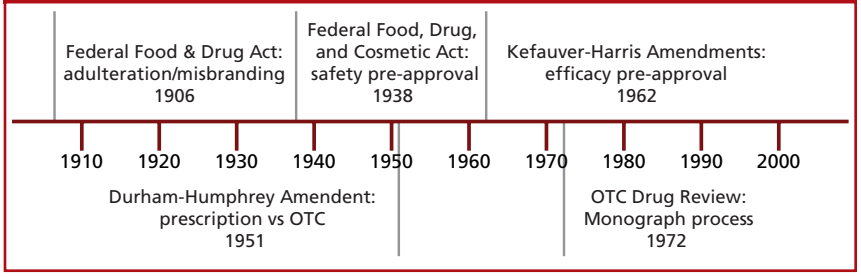
USP is in the process of updating its compendial monographs and FDA applauds this change, which will help improve the standards companies follow when making drug products. In fact, the agency, along with the Consumer Healthcare Products Association (CHPA), is working closely with USP on the pharmacopeial convention's monograph modernization project, which began in 2010. The aim is to update key USP compendial monographs (to clarify, these are different from FDA's OTC monographs) to incorporate modern analytical methods and technologies.

The most significant gaps reside in USP monographs that have relatively nonspecific identification and/or assay procedures and in monographs lacking procedures for impurities and degradants, says Karen Russo, vice-president for small molecules at USP. In addition to these gaps, methods for certain procedures are outdated (e.g., packed column gas-chromatography and wet-chemistry techniques) and need updating.

Furthermore, USP notes that only about 25% of the monographs targeted for revision are OTC-related. Although, says USP, it's important to note that the same product or active pharmaceutical ingredient can be used in OTC and prescription form based on the dose or other FDA criteria.

In February 2011, the standard-setting body said it would be focusing on a few specific OTC monographs based on an FDA request. The agency asked USP to make a priority the monographs for acetaminophen and diphenhydramine (as well as copovidone, crospovidone, povidone, and talc) based on potential health concerns with these drugs (4).

Figure 1: More than 250,000 over-the-counter (OTC) products are available to consumers. There are more than 80 therapeutic categories of OTC drugs, ranging from cough and cold medications to sleep and gastrointestinal aids. The following timeline provides a detailed look at the history of OTC regulation. (Adapted from an FDA online presentation from Ref. 1)



"Acetaminophen- and diphenhydramine-containing drug products are two of the highest-volume selling OTC monograph drugs," explains FDA's Kubaska. "There are known impurities in both of these drugs that represent known (acetaminophen) and theoretical (diphenhydramine) concerns with respect to toxicity. So, the extent of exposure (using sales volume as a surrogate) and toxicity concerns played key roles in the selection of these drugs…."

Adds Russo, "The challenge with diphenhydramine and acetaminophen are the many drug products, particularly those combined with other drugs, and the variety of dosage forms, such as tablets and oral liquids. For example, there are more than 25 acetaminophen-containing dosage form monographs in the *USP–NF* representing primarily OTC drugs."

Another challenge to the project overall, says Russo, is finding the replacement procedures for those monographs that need revision. "We encourage manufacturers to submit their procedures to USP so that the monograph can be revised to incorporate the new procedure(s)…. USP is ... using its own laboratory resources to the extent possible to develop and validate procedures to serve as the basis for the monograph revisions; however, we are not able to accomplish this on our own." In addition, says Russo, USP has to find procedures that can accommodate all manufacturers of a given drug substance or drug product.

There is no set deadline for completing the monograph project, according to USP, although a general target is to finish before the 2010–2015 convention cycle ends. USP is hosting an OTC workshop in September 2011 to discuss with industry and FDA some of these compendial issues. (For more details on the monograph modernization project, see the Inside USP column on page 90.)

Labeling clarifications

Meeting regulatory requirements and safety standards is only half of the battle for OTC drug manufacturers. As FDA's Kubaska points out, "Like prescription drugs, OTC drugs can cause serious adverse events." And the fact that there is no healthcare provider between a consumer and an OTC drug means that "the consumer must be able to self-diagnose the condition and safely self-medicate," explains Kubaska. For this reason, OTC product labels and information leaflets must be even more clearly identifiable, readable, and understandable to the average consumer than those for prescriptions.

According to David C. Spangler, senior vice-president of policy, and general counsel and secretary for CHPA, "the labeling standards that we have today [for OTCs] have been gone over in painstaking detail by FDA. When putting together a category monograph, the biggest thing FDA is focusing on, in addition to effectiveness and safety of the ingredients, is getting the labeling right. There is always room for improvement, but labeling reviews have been going on for decades."

In terms of improvement, in August 2010, FDA released an OTC guidance for industry on label-comprehension

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studies (5). These studies determine how well a consumer can read and understand a label. "FDA felt the need to publish this guidance to help industry conduct well-designed studies that provide meaningful data," says Kubaska. Although the guidance is not expected to require major changes in industry practice, it demonstrates that regulators are concerned about making sure OTC manufacturers provide the most clear and accurate information to consumers.

The guidance targets companies planning a label-comprehension study to evaluate a new label or a labeling change, but also applies to drug sponsors trying to switch their already approved prescription drugs to nonprescription status, a trend that seems to be on the rise, says CHPA's Spangler. (See a list of prescription to nonprescription switches at http://chpa-info.org/media/resources/r_4620.pdf.) This type of marketing switch has to be done extremely carefully, not just from a manufacturing and business perspective, but also from the consumer's perspective.

Caution is especially important when considering a complex drug status switch, such as those for cholesterol-lowering products. According to Spangler, these types of status switches involve intense labeling reviews because the products they are based on are generally for asymptomatic conditions. Without obvious symptoms, it is more difficult for a consumer to self-diagnose and self-treat, and so the product labels must be extremely detailed. "We are already seeing this type of switching activity in the UK, and it's more likely for the US in the future."

Across the Atlantic, the European Medicines Agency (EMA) is taking another look at OTC product labels as well. In April 2011, the agency released quality review recommendations for nonprescription-drug packaging design and labeling that would apply across the European Union (6). The new recommendations add to already existing requirements in the European Commission's Directive 2001/83/EC and in the 2009 EMA guideline on the readability of the labeling and package leaflet of medicinal products for human use (7). The new document aims to better harmonize OTC labels across Europe, especially where certain descriptions may use symbols or pictograms. Fonts, colors, text size, and information to be included on the labels and leaflets are addressed. Comments on the recommendations are due to EMA by June 30, 2011.

Inspections

FDA aims to inspect prescription and nonprescription drug-manufacturing facilities every two years (8). OTC facility inspectors focus on verifying drug-monograph compliance (3). Many of the drug recalls that have occurred during the past 18 months are not tied to FDA approval or labeling, but rather to the manufacturing and supply-chain management of these products, points out Jonathan M. Lewis, a princi-

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pal at Advanced Biomedical Consulting. "Many OTC drugs are less 'risky' in FDA's eyes," he says, "so these facilities often are not inspected nearly as frequently or with as much focus as compared with prescription products, such as injectables."

Lewis suggests that preapproval inspections, which he says are rarely required for OTC drug products, be implemented. "These inspections would help assess manufacturing conditions and regulatory compliance prior to marketing of these products," he says.

Ravi Harapanhalli, principal consultant and late-stage services lead at Parexel Consulting, agrees. "Over the counter drugs approved *via* an NDA/ANDA process don't need anything beyond what is currently applied with regard to ensuring product quality. However, for monograph drugs, a requirement for cGMP inspection prior to marketing should be mandated to ensure appropriate product quality and postmarketing recalls. If FDA cannot have the resources to do inspections, it should consider third-party audits as an alternative for OTC drugs marketed under monographs. A system of third-party audits is already accepted for certain low-risk devices."

Also, says Harapanhalli, "OTC drugs approved under an NDA or ANDA pathway seem to have fewer concerns of product quality compared with the OTC drugs marketed under monographs. Because monograph drugs are neither pre-reviewed nor approved, a manufacturer takes full responsibility to attest that their product meets the quality guidelines and requirements described in an OTC monograph."

This responsibility can be more difficult for smaller manufacturers of OTC products, adds Lewis. These smaller firms often turn to outsourcing and do not have the finances or staff to audit their contract manufactures and suppliers. They end up taking "more risk, often at the cost of quality, to produce these products domestically," says Lewis.

Resources are a constant challenge for FDA as well. Harapanhalli points out that many cGMP inspections of OTC sites

contin. on 105

Behind the Counter

Christopher Allen and Angie Drakulich

While improvements are made to over-the-counter (OTC) drug monographs and labels, some groups are pursuing a third class of drugs called "behind-the-counter" (BTC) drugs. Currently, there are two classes of drugs in the US: prescription and nonprescription (i.e., OTC). BTC is defined by the US Government Accountability Office (GAO) as a class of nonprescription drugs that is available only in pharmacies and that requires contact with a pharmacist (1).

A 2009 GAO study analyzed the pros and cons of a BTC class of drugs after examining documents and consulting with pharmaceutical experts in five countries (the US, Australia, Italy, The Netherlands, and the United Kingdom) (1). According to the report, proponents of a BTC class laud the potential for increased availability of nonprescription drugs, and thus, a decrease in healthcare costs. If certain drugs switch from prescription to nonprescription status to enter the BTC class, their prices may decline. In addition, physician visits may be reduced because prescriptions will not be required for these drugs. (1).

On the other hand, opponents fear a rise in out-of-pocket expenses for consumers if third-party payers elect not to cover BTC drugs. Additionally, they are wary that pharmacists might not be adequately equipped to offer the same high quality services and informed recommendations that a medical professional is trained to handle (1).

The most notable example of the BTC movement is that of Teva's emergency contraceptive drug, Plan B. In 2006, BTC sales began for Plan B for women age 18 and above (2) (the age was subsequently lowered to 17 in April 2009). A pharmacist must check the consumer's proof of age before dispensing the prescription product (3). In 2009, the new single-dose Plan B One-Step was cleared for BTC availability as well (4).

Other recent laws have justified a BTC drug class by citing public safety. The Combat Methamphetamine Epidemic Act of 2005, for example, imposed national purchasing limitations on drugs containing pseudoephedrine (PSE) (i.e., a maximum daily limit of 3.6 grams per purchaser). PSE, a decongestant, is the active ingredient in Sudafed, which is used to relieve cold symptoms. However, it is also an essential ingredient of the illicit chemical production of methamphetamine, a highly dangerous and addictive Class A narcotic. Employees selling the products must keep a log of the product and quantity sold, names and addresses of purchasers, and dates and times of the sales (5).

Opponents still have their doubts about a third drug class, however. "It would restrict access to drugs rather than expand access," explains David Spangler, senior vice-president of policy and international affairs at the Consumer Healthcare Products Association (CHPA). "If an OTC product is safe enough to pass FDA review, and the label is clear enough per the guidelines, a consumer ought to have the right to buy a product anywhere and at the time of [his or her] choosing," he says.

Jonathan M. Lewis, a principal at Advanced Biomedical Consulting, agrees, "Another layer of regulatory classification would snowball new regulations and amendments… that could cause confusion for industry, consumers, and even FDA." As a result, says Lewis, the benefit of a BTC class may not outweigh the cost.

Regulatory debates involving patients' rights, drug prices, and ethics continue to cloud the gray area surrounding a potential BTC class. According to an FDA spokesperson, "If drug products are eventually placed behind the counter, FDA will need to consider how the consumer–pharmacist interaction impacts the requirements for the demonstration of safety and effectiveness of drugs."

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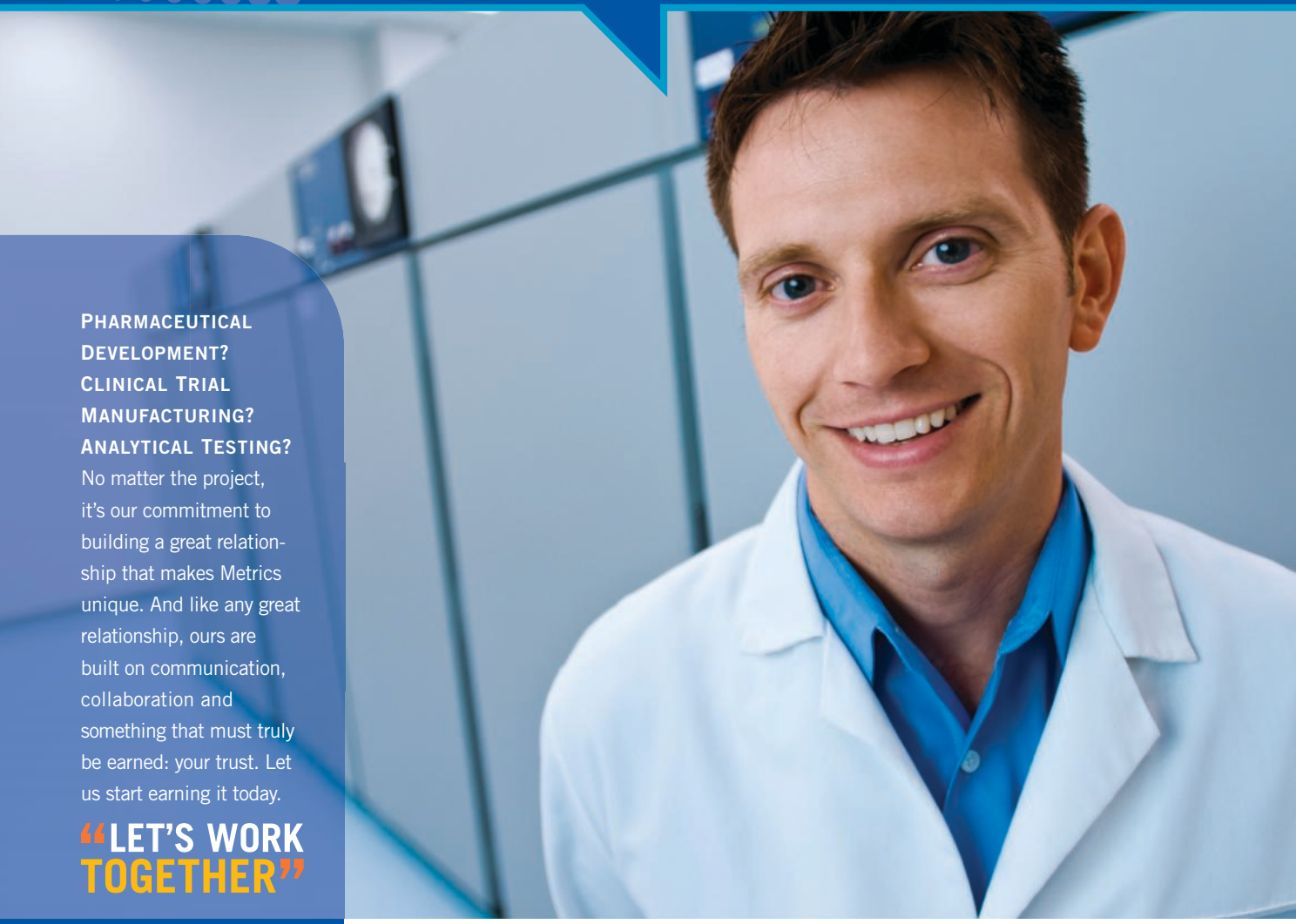

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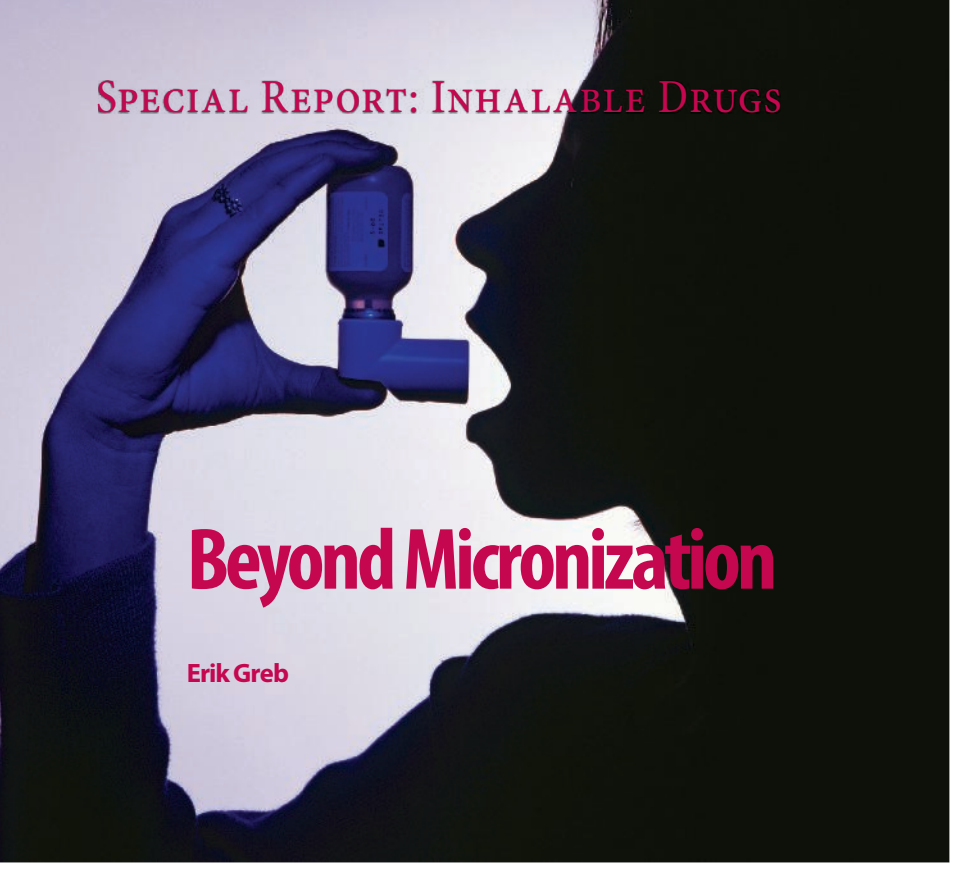

Beyond Micronization

Erik Greb

Emerging methods could provide alternative ways of producing inhalable drug particles.

Ask any manufacturer what process it uses to make inhalable drug particles, and the answer is likely to be micronization. This process has been the industry standard for decades, but it is not necessarily ideal. For starters, micronization is not well understood. In addition, a certain amount of material is lost during the process, so its final yield may not be optimal. Given these conditions, manufacturers have good reason to look for alternative processes for making inhalable medicines. Fortunately, several emerging methods show promise.

Particle replication in nonwetting templates

In 2005, researchers at the University of North Carolina (UNC) at Chapel Hill developed a technology called Particle Replication in Nonwetting Templates (PRINT). The method is based on the computer industry's procedure for making transistors, says Joseph DeSimone, professor of chemistry at UNC and leader of the research team. Using established technology, the researchers made etched silicon wafers to serve as templates for drug particles with previously determined characteristics. Using a template enables manufacturers to design the size and shape of their drug particles precisely, to target the upper airway or the alveolar sacs effectively, for example.

To scale up production, the team made a drum to pattern a print mold made of film that can be from 6 to 24 in. wide. The drum can make thousands of linear feet of molds, depending on the number of particles required.

After the molds are complete, their cavities are filled with the inhalable formulation, which can include the active ingredient alone or with excipients. Particles are harvested by adhesive films.

The PRINT technique, which complies with cGMP, can create traditional and large-molecule drugs for various diseases, including respiratory ailments such as cystic fibrosis and chronic obstructive pulmonary disease. The method also could be used to manufacture particles to fight bacterial infections or deliver chemotherapeutic agents to the lung. The researchers are interested in targeting the central nervous system through inhaled particles made using the PRINT process, says DeSimone.

A significant advantage of the PRINT method is that it consistently yields uniform populations of particles. "There's essentially no dispersion in size and shape. That's not been available before," says DeSimone.

The technology also lets formulators create particle sizes and shapes that traditional methods have not generated successfully in the past. For example, DeSimone's team has made cylindrical particles that are 80 nm in diameter, and they can achieve particle sizes as large as 5 μm. The team is also using PRINT to develop particles that can rotate automatically in a low-velocity airstream, much like a maple seed does when it falls from a tree. "We're getting into characteristics that have never been designed into a respiratory drug therapy," says DeSimone.

It's hard to achieve this kind of mixture through traditional particle approaches, such as spray drying from a solution, because ingredients in various phases tend to separate, and the processes give operators little latitude

IMAGE: INFLUX PRODUCTIONS, PHOTODISK, GETTY IMAGES

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for controlling the ratio of matrix to drug. "With PRINT, we can precisely tailor the ratio of those two components because we're simply filling a cup," says DeSimone. The high level of control that PRINT offers could help manufacturers create multicomponent particles for targeted delivery.

On the other hand, risk-averse drug manufacturers could consider the PRINT technique's novelty a liability. Companies might be inclined to use micronization because they are familiar with that process. Also, the throughput of the PRINT technique, which has a two-dimensional format, is lower than that of volumetric processes such as spray drying.

Nevertheless, the PRINT technique shows great promise for manufacturing inhalable drug particles, according to DeSimone. The method can enable continuous manufacturing; provide control of size, shape, and chemical composition; enhance drug stability; and enable particles to be made from otherwise challenging formulations.

Supercritical-fluid technology

Supercritical-fluid technology, a more established method than PRINT, may soon be used to manufacture an FDA-approved drug. MAP Pharmaceuticals has been producing Levadex, its orally inhaled migraine therapy, through supercritical-fluid crystallization. The company completed clinical development for the drug last year and will submit a New Drug Application during the first half of 2011, according to the Form 10-K filed on Mar. 4, 2011.

Supercritical-fluid technology has been around for more than a century, and it is a common method for making decaffeinated coffee. In the mid 1990s, the pharmaceutical industry began examining the technique as a way of manufacturing drug particles. Because the process is rapid, and because no solvent is present during crystallization, drugmakers thought that supercritical-fluid technology could yield uniform particles.

Supercritical fluids could be considered a fourth state of matter that combines the properties of liquids and gases. These fluids can act as solvents or antisolvents. Carbon dioxide becomes a supercritical fluid when it is heated above 31.1 °C and held at a pressure higher than 73.8 bar. Because of these characteristics, carbon dioxide has become the most common supercritical fluid in the pharmaceutical industry.

Supercritical antisolvent precipitation (SAS) is one way to produce inhalable drug particles. In this method, a solution of drug and organic solvent (e.g., budesonide in ethanol) is introduced into a flow of supercritical carbon dioxide, which extracts the solvent rapidly from the drug solution. The drug substance then becomes supersaturated and forms particles in milliseconds. Variations in SAS processes are distinguished by the ways in which the drug solution and supercritical fluid interact. Some SAS processes are more efficient than others, but each of them yields dry powders in a single step.

Respirable drug particles processed through supercritical antisolvent precipitation.

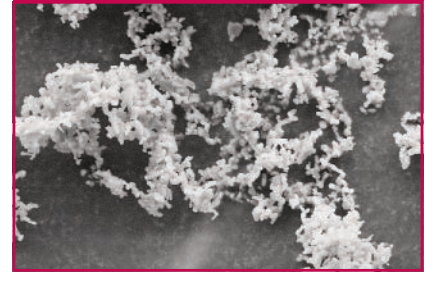


IMAGE IS COURTESY OF PETER YORK

Because carbon dioxide's critical temperature is not much different from ambient conditions, SAS is an attractive method for processing pharmaceuticals, says Peter York, chief scientist at CrystecPharma and *emeritus* professor of physical pharmaceutics at the University of Bradford, United Kingdom. The process yields dry powders without additives or residual solvents that might be unacceptable to regulators.

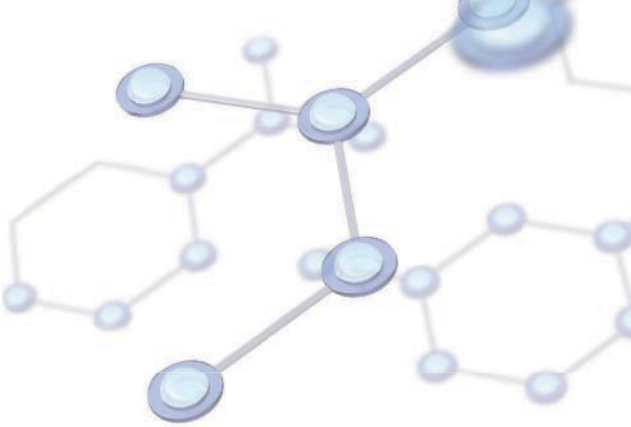
In addition, SAS results in particles that have highly desirable properties for inhalation medicines. The particles generally are smaller than 10 μm and have a narrow size distribution. The process is tunable and can make 1–3-μm particles (e.g., for targeting the deep lung) or 3–5-μm particles (e.g., for targeting the upper respiratory airways). Particles made through SAS also are highly crystalline, free from amorphous domains, and, thus, highly stable. The particles' surfaces tend to be smooth and regular with low surface energy, and these characteristics reduce agglomeration and help improve downstream handling.

In the past 15 years, technology has advanced to the point where SAS can produce materials at manufacturing scale that comply with cGMP. New developments at CrystecPharma enable composite particles containing defined ratios of two or more drug substances (e.g., for combined drug therapy) to be manufactured. Clinical evidence indicates that SAS improves the performance of drug materials, compared with other manufacturing techniques. Products containing SAS-processed particles have improved drug bioavailability, led to simplified formulations, and reduced required doses, says York.

SAS also is superior to micronization in several ways. During micronization, particles are bombarded against the walls of a mill, and this intensive process can create high-energy sites on the surfaces of the materials being milled. These high-energy sites can cause potential chemical or physical changes in the material. One of the most problematic changes is the introduction of noncrystalline or amorphous domains in the product, which can reduce its stability. Micronized material also has highly charged surfaces and tends to be cohesive and difficult to disperse into an aerosol, says York.

Yet many drugmakers might be reluctant to abandon micronization because they have years of experience with the process—and have invested considerable sums into the technology and training required. The industry's overall conservatism and antipathy to change also could slow companies' adoption of SAS, in spite of the method's advantages.

If FDA approves Levadex, however, it would be the first product on the market manufactured through SAS. "That will take the risk out of these processes for a lot of potential clients," says York. **PT**



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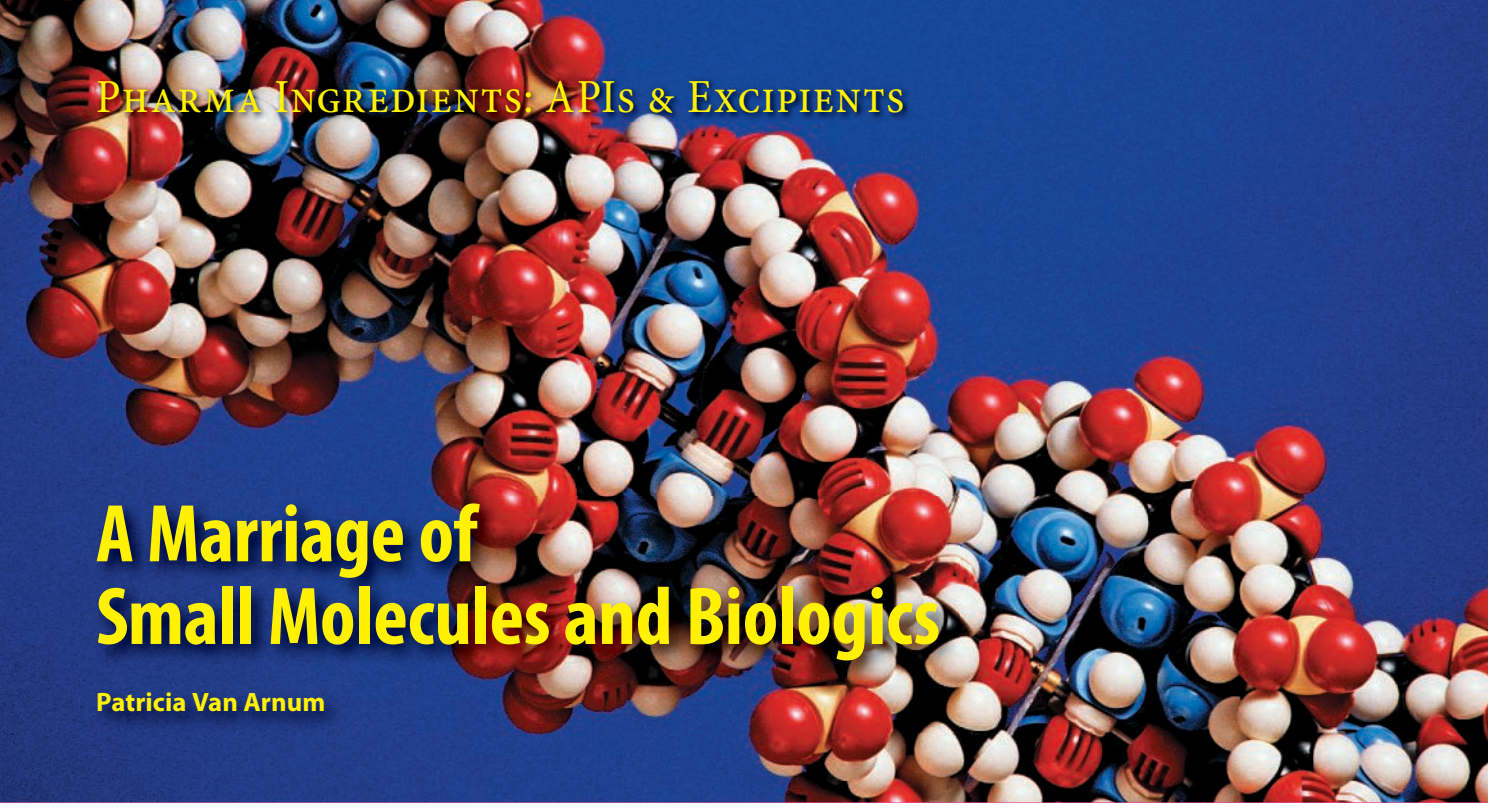

A Marriage of Small Molecules and Biologics

Patricia Van Arnum

Approaches in using methods in small-molecule and peptide synthesis offer promise in widening the scope of drug candidates.

The ongoing task of drug development is to move promising discovery candidates into commercial production. Different modalities of small-molecule or biologic-based drugs offer relative advantages and disadvantages in achieving these goals. Recent efforts in drug development seek to marry the best of both modalities with specialized approaches, such as stapled peptides and other improvements in peptide synthesis.

Stapled peptides

Stapled peptides use peptide-stabilization technology to enhance potency and cell permeability of a drug. Although the concept of stapled peptides is not new, stapled peptides as a field came into greater prominence last year when Roche signed a drug-development deal worth up to $1.1 billion with the biopharmaceutical company Aileron Therapeutics to discover, develop, and commercialize stapled peptides. Under the agreement, which was announced in August 2010, Roche is guaranteeing at least $25 million in funding for technology-access fees and continued research and development efforts by Aileron. The company is eligible to receive up to $1.1 billion in payments based on discovery, development, regulatory, and commercialization milestones if drug candidates are developed for five undisclosed drug targets in the following areas: oncology, virology, inflammation, metabolism, and central nervous system.

Stapled peptides are designed to address pharmacological limitations of small molecules and existing biologics in intracellular protein–protein interactions. Although small molecules are able to penetrate cells, the large binding surfaces for intracellular protein–protein interactions often make small-molecule modulators ineffective. Although peptides and proteins have the size and functionality to effectively modulate intracellular protein–protein interactions, they often do not permeate cells and therefore are used to modulate extracellular targets such as receptors (1). These limitations of small molecules and existing biologics make a vast array of potential drug targets "undruggable." Approximately 80% of potential drug targets are considered "undruggable" by either modality (1, 2).

Peptides face certain limitations as drugs. They lack the ability to enter cells, are inherently unstable within the body, are rapidly broken down into inactive fragments by circulating enzymes, such as proteases, and are quickly filtered from the bloodstream by the kidneys. Stapled peptides seek to resolve those problems. Because many "undruggable" therapeutic targets include those protein–protein interactions in which α-helices are required in lock-and-key-type mechanisms, an approach is to design α-helical peptides that have structural and functional properties that enable them to penetrate into the cell, bind to the therapeutic target, and modulate the biological pathway (1).

Aileron stabilizes peptides by "stapling" them with hydrocarbon bonds into an α-helix. Once constrained in the α-helix structure, the peptides are protected from degradation by proteases. The stabilized α-helical peptides can penetrate cells by energy-dependent active transport and

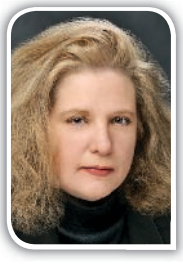

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IMAGE: M. FREEMAN/PHOTOLINK, GETTY IMAGES

typically have a higher affinity to large protein surfaces (1, 2).

Aileron was cofounded in 2005 by Gregory L. Verdine, chair of Aileron's scientific advisory board, professor of chemistry at Harvard University, director of the Harvard/Dana–Farber Program in Cancer Chemical Biology, and executive director of the Chemical Biology Initiative at the Dana–Farber Cancer Institute. In 2006, Aileron acquired exclusive rights from Harvard University and the Dana–Farber Cancer Institute to develop and commercialize a drug-discovery pipeline of stapled peptides. In 2006–2007, Aileron licensed rights from the fine-chemicals and technology firm Materia for catalysts used in olefin metathesis. Materia holds the rights to the olefin metathesis technology developed by Robert H. Grubbs, professor at the California Institute of Technology, who was awarded the Nobel Prize in Chemistry in 2005 with Richard R. Schrock and Yves Chauvin for their work in olefin metathesis using ruthenium-based catalysts. Part of the reaction scope of olefin metathesis is ring-closing metathesis (RCM), which transforms a diene into a cyclic alkene and is used to create macrocycles, including bioactive cyclic peptidomimetics. Grubbs was one of the first to offer research describing RCM to tether residues of helical peptides (3, 4).

In 2008, Aileron acquired exclusive rights from New York University for additional methods to stabilize peptides and peptidomimetics. In 2009, Aileron received $40 million in venture capital funding, which included funding from four pharmaceutical venture-capital funds: SR One (GlaxoSmithKline's venture capital fund), the Novartis Venture Fund, Lilly Ventures (Eli Lilly's venture capital fund), and the Roche Venture Fund.

Verdine recently spoke at the American Chemical Society's (ACS) National Meeting & Exposition in Anaheim, California, in late March 2011, to provide an update of his research at Harvard with respect to stapled peptides. "Our stapled peptides can overcome the shortcomings of drugs of the past and target proteins in the body that were once thought to be undruggable," he said in a Mar. 28, 2011, ACS press release. "They are a genuinely new frontier in medicine."

Verdine highlighted two stapled-peptide drug candidates that respectively target colon cancer and asthma. The colon-cancer stapled peptides inhibit activity of the protein β-catenin, which when present in a hyperactive form, causes cell to grow in an uncontrolled way. This protein has been linked with an increased risk of colon cancer and other types of cancer, including skin, brain, and ovarian cancer. When introduced to human colon cancer cells in laboratory cultures, the stapled peptides reduced the activity of β-catenin by 50%, according to the ACS release.

In a second development, Verdine reported on what he identified to be the first stapled cytokines for treating asthma. Cytokines are hormone-like proteins secreted by the cells of the immune system and other body systems that help orchestrate intercellular signalling. The stapled cytokines moder-

Formulation development forum: nanosponges

Creating or improving systems for targeted drug delivery is an area of ongoing research, and is an area of particular importance to delivering anticancer therapeutics. Researchers at Vanderbilt University and Emory University recently reported on a controlled-release nanoparticle drug-delivery system, which may be an improved delivery method for delivering anticancer therapies, including direct injection into a tumor site.

The system, dubbed a "nanosponge," uses a nanoparticle-sized system to deliver the drug payload. These nanoparticles circulate in the body until they encounter the surface of a tumor cell, where they adhere to the surface and begin releasing the drug in a controllable and predictable fashion. The controlled-release nanoparticle drug-delivery system used a targeting peptide that recognized a radiation-induced cell-surface receptor. This targeting agent combined a recombinant peptide with a paclitaxel-encapsulating nanoparticle that specifically targeted irradiated tumors, thereby increasing apoptosis and tumor-growth delay. A Phage display biopanning identified Gly-Ile-Arg-Leu-Arg-Gly (GIRLRG) as a peptide that selectively recognizes GPR78, a receptor on certain tumor cells. Antibodies to GRP78 blocked the binding of GIRLRG *in vitro* and *in vivo*. The conjugation of GIRLRG to a sustained-release nanoparticle drug-delivery system increased paclitaxel concentration and apoptosis (1)

When loaded with an anticancer drug, the delivery system is three to five times more effective than direct injection at reducing tumor growth (2). The sponge acts as a three-dimensional network or scaffold. The backbone is a long-length polyester. It is mixed in solution with crosslinkers to form the polymer. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in the body. As it breaks down, it releases its drug payload in a predictable fashion (2).

Targeted delivery systems of this type have several basic advantages. Because the drug is released at the tumor site instead of circulating widely through the body, it should be more effective for a given dosage. It also should have fewer harmful side effects because smaller amounts of the drug come into contact with healthy tissue. Another advantage is that the nanosponge particles are soluble in water. Encapsulating the anticancer drug in the nanosponge allows the use of hydrophobic drugs that do not dissolve readily in water. Currently, these drugs must be mixed with adjuvant reagents, which potentially can reduce the efficacy of the drug or cause side effect (2).

The nanosponge is produced through fairly simple chemistry. The researchers developed simple, high-yield so-called "click chemistry" methods for making the nanosponge particles and for attaching the linkers. The drug used for the animal studies was paclitaxel, the active ingredient in the anticancer therapy Taxol. The researchers recorded the response of two different tumor types—slow-growing human breast cancer and fast-acting mouse glioma—to single injections. In both cases, they found that the delivery through nanosponges increased the death of cancer cells and delayed tumor growth compared with other chemotherapy approaches.

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ate the activity of the cytokine, interleukin–13, which asthma patients produce in abnormally large amounts that contribute to asthma attacks, according to the ACS release.

In another development, researchers at the Dana–Farber Cancer Institute, Children's Hospital in Boston, and Harvard University recently reported the use of hydrocarbon double-stapling to remedy the proteolytic instability of a lengthy peptide (5). Specifically, the researchers applied the stapled approach to Fuzeon (enfuvirtide), a 36-amino-acid peptide that inhibits human immunodeficiency virus Type 1 (HIV-1) infection by targeting the viral fusion apparatus.

Fuzeon is marketed by Roche, which developed the drug with the biopharmaceutical company Trimeris. Roche is responsible for the manufacture, sales, marketing, and distribution of Fuzeon. Roche manufactures bulk quantities of Fuzeon drug substance in its Boulder, Colorado, facility and produces finished drug product from bulk drug substance at other Roche facilities, according to Trimeris' 2010 annual filing with the US Securities and Exchange Commission. The finished drug product is shipped to another Roche facility for distribution. The drug had 2010 sales of $88 million.

The researchers noted that enfuvirtide is used as a salvage treatment option because of poor *in vivo* stability and poor oral bioavailability. To address the proteolytic shortcomings of long peptides as therapeutics, the researchers studied the biophysical, biological, and pharmacological impact of inserting all-hydrocarbon staples into the drug (5). The researchers found that the peptide double-stapling created protease resistance and improved pharmacokinetic properties, including oral absorption. The hydrocarbon staples created a "proteolytic shield" by reinforcing the overall α-helical structure, which slowed the kinetics of proteolysis and also created a complete blockade of peptide cleavage at the constrained sites in the immediate vicinity of the staple (5). The researchers noted the potential of double-stapling to other lengthy peptide-based drugs.

Earlier this year, researchers at the University of Buffalo reported ways of stapling peptide helices. Their approach, dubbed "photoclick stapling," involves the photo-induced 1,3-dipolar cycloaddition reactions (i.e., photoclick chemistry) involving small-ring heterocycles and simple alkenes for both *in vitro* and live-cell applications. The researchers specifically reported on the photo-induced 1,3-dipolar cycloaddition reaction to staple a peptide dual inhibitor of the p53–Mdm2/Mdmx interactions. The researchers reported that a series of stapled peptide inhibitors were efficiently synthesized and showed dual inhibitory activity in an enzyme-linked immunosorbent assay. The positively charged, stapled peptides showed enhanced cellular uptake along with modest *in vivo* activity (6). In addition to extending the stapled peptide approached targeting p53–Mdm2/Mdmx interactions, the researchers also are examining BH3–Bcl2/Bcl–xL interactions as potential anticancer therapies.

Stapled peptides could open up a whole host of new targets for therapies.

"There is a lot of potential here." said Qing Lin, assistant professor at the University of Buffalo and lead researcher, in a Feb. 5, 2011, University of Buffalo press release. "Our chemistry is unique. There are not many new drug targets out there today, which partly explains the declining number of FDA-approved new drugs in recent years. So there's a need to come up with new technologies that can overcome this barrier. To this end, stapled peptides could open up a whole host of new targets for therapies."

Other approaches

Improving peptide synthesis also is an area of ongoing research. Researchers from Vanderbilt University recently reported their efforts in overcoming a limitation in peptide synthesis, the incorporation of non-natural amino acids into the peptide chain. The researchers noted that creation of amide bonds typically use methods that principally are based on dehydrative approaches or oxidative and radical-based methods. Generally, carbon and nitrogen bear electrophilic and nucleophilic character, respectively, during the carbon–nitrogen bond-forming step. In their work, the researchers showed the activation of amines and nitroalkanes with an electrophilic iodine source to directly make amide products. The suggested mechanism showed that the polarities of the two reactants were reversed during carbon–nitrogen bond formation relative to traditional approaches. Looking forward, the researchers noted that using nitroalkanes as acyl anion equivalents provides a conceptually innovative approach to amide and peptide synthesis, and one that may further engender more efficient peptide synthesis that relies on enantioselective methods (7).

"Scientists from many disciplines have sought improved methods to streamline the synthesis of peptides through purely chemical means in order to increase the diversity of the chemical tools available for the design of improved therapeutics," said Jeff Johnston, professor of chemistry at Vanderbilt University, in a June 23, 2010, Vanderbilt University press release. "Our discovery of a conceptually new approach to peptide synthesis brings this capability much closer to reality."

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Gelatin Capsule Shell Cross-Linking

Tier II Dissolution Method Development in the Presence of Sodium Lauryl Sulfate

Xiling Song, Yong Cui, Minli Xie

Cross-linking in hard gelatin capsule shells is a common cause of slowdown in Tier I dissolution testing; however, direct addition of purified pepsin to the medium, as described in *USP* <711>, may not always be a solution if the medium contains sodium lauryl sulfate (SLS). The author develops a practical approach to avoid unwanted interaction between pepsin and SLS in dissolution Tier II tests.

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Hard gelatin capsules are a common solid oral dosage form, but exposure to accelerated conditions, e.g. 40 °C and 75% relative humidity (RH), can cause capsule shell cross-linking. Capsule shell cross-linking arises from gelatin polymerization, a process facilitated by high temperature, high humidity, ultraviolet (UV) and visible irradiation, dyes, and aldehydes (1–4). The main impact of gelatin cross-linking is prolonged capsule disintegration time, and a subsequent slow-down of drug product dissolution rate. In the event that hindered dissolution arises from gelatin cross-linking and the product fails specification, *USP* <711> recommends the addition of enzymes (e.g., pepsin) to the dissolution medium to serve as the Tier II dissolution test (5). It is important, though, to confirm that dissolution failure is a direct outcome of cross-linked gelatin shells rather than degradation of drug product performance.

Sodium lauryl sulfate (SLS) is a surfactant commonly used in dissolution medium to improve the solubility of poorly water-soluble drugs. The presence of SLS in dissolution medium deactivates pepsin, which complicates the Tier II method described above (6). One option would be to redevelop the dissolution method and abandon SLS. But this option could be costly in time and resources, and may discourage the use of SLS in capsule formulations in general, despite its excellent solubilizing capability, low cost and ease of use. Performing Tier II dissolution tests in the presence of SLS is considered beneficial to the development and quality control of capsule formulations.

This article will detail the experimental procedures and the study results of a case where the above issues were encountered and tackled in the development of a capsule formulation. A slowdown in dissolution rate was discovered for the gelatin capsule formulation when it was stored at accelerated conditions of 40 °C and 75% RH for three months.

Materials

Size one opaque hard gelatin capsule shells were purchased from Capsugel. Dissolution was performed using *USP* Apparatus II (paddles), Model VK 7000 (Varian). Stand-alone UV–Vis spectrometer with diode array capacity, Model 8453, was from Agilent. Capsule sinkers (size 8/23) were from Sotax. SLS (reagent

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Table I: Dissolution results for capsules stored at 40 °C and 75% relative humidity (RH) for 1 and 3 months.

	% Release					
	Time Point	**Mean (n = 6)**	**SD**	**%RSD**	**Minimum**	**Maximum**
t = 1 Mon	10 min	60.9	1.1	1.8	59.6	62.5
	20 min	76.2	1.9	2.5	73.5	79.3
	30 min	83.7	2.4	2.9	80.3	86.7
	45 min	89.5	2.4	2.7	86.5	92.3
	60 min	93.0	2.0	2.2	90.6	95.4
	Infinity	97.1	1.0	1.0	95.3	97.8
	Time Point	**Mean (n = 12)**	**SD**	**%RSD**	**Minimum**	**Maximum**
t = 3 Mon	10 min	47.1	15.7	33.3	20.0	63.5
	20 min	64.6	16.5	25.6	32.5	80.4
	30 min	73.1	16.9	23.1	41.2	88.9
	45 min	80.5	16.5	20.5	47.7	94.7
	60 min	84.8	15.7	18.5	52.3	97.7
	Infinity	98.5	2.1	2.1	95.7	101.0

SD is standard deviation. RSD is relative standard deviation.

grade > 99%) was purchased from Fisher Scientific. Full flow cannula filters (10 µm) were from Quality Lab Accessories. Pepsin (800–2,500 units/mg) purified from porcine gastric mucosa was purchased from Sigma-Aldrich. All other chemicals were ACS grade or equivalent.

Methods

Dissolution methods. Tier I dissolution was performed using *USP* paddle apparatus in 900 mL of 0.01 N HCl with 1.0% SLS in each vessel at 37 °C. The paddle rotation speed was 75 rpm.

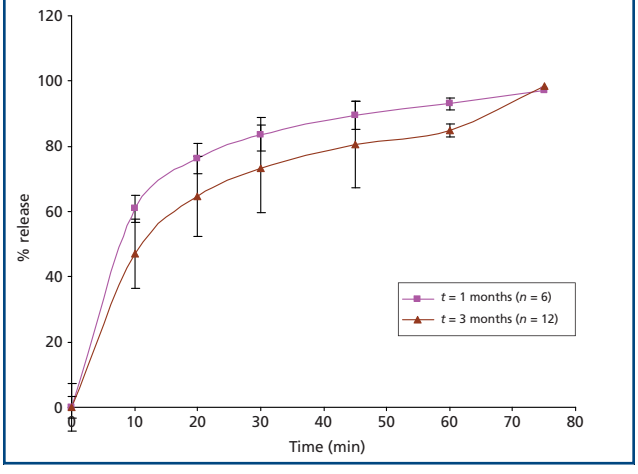
Samples were obtained at predetermined time points of 10, 20, 30, 45, and 60 min. After 60 min the paddle speed was increased to 250 rpm for another 15 min before samples at the "infinity" time point were withdrawn. All samples were analyzed using a UV–Vis spectrometer at a wavelength of 266 nm.

The initial Tier II dissolution method was developed following *USP* <711>, using a premixed medium containing 900 mL of 0.01 N HCl, 1.0% SLS and 750,000 units/L purified pepsin in each vessel.

The final Tier II dissolution method was modified from *USP* <711> by using 600 mL of 0.01 N HCl solution containing 750,000 units/L of purified pepsin in each vessel at the beginning of the test. After 5 min, an additional 300 mL of 0.01N HCl solution containing 3.0% SLS was added to each vessel. This medium was preheated and kept at 37 °C before transferring. Other method conditions were constant

Capsule switching test procedure. To identify the cause of dissolution slowdown, a capsule switching test was conducted. The contents of six capsules, which had been stored at 40 °C and 75% RH for three months and showed dissolution slow down, were fully transferred into six fresh shells. The fresh capsule shells were from the same batch as those used in the stability study and were stored in a closed container at ambient conditions. The six emptied (i.e., aged) capsule shells, on the other hand, were refilled with a fresh drug blend made with the same formula and manufacturing process.

Figure 1: Dissolution profiles for capsules stored at 40 °C and 75% relative humidity for 1 and 3 months.



Results and discussion

Table I and Figure 1 provide the dissolution results and profiles of capsules stored at 40 °C and 75% RH for one and three months, respectively. Testing was performed using the Tier I method. Results should conform to a Q value of 70% at 45 min. Comparing the two sets of data, it is clear that capsules stored for three months had significant variation. Four out of twelve capsules had release of 73.0%, 66.2%, 47.7%, and

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53.1%, respectively. The results did not meet Stage I or Stage II criteria.

The observation of reluctant capsule shell rupture was a good indication that dissolution failure was most likely caused by cross-linked capsule shell rather than drug performance. To further confirm this theory, an investigation in which capsules were switched and subjected to dissolution testing using Tier I was performed. Dissolution data for switched capsules are provided in Table II; data for fresh drug blend in fresh capsule shells are included for comparison. As expected, the capsules with fresh drug blend in aged capsule shells had individual low results and significantly high variation at every time point. The capsules with either old or fresh blend in fresh capsules shells both had satisfactory results. The study results proved that the aged capsule shells, rather than product-quality change, caused the original dissolution failure.

For hard gelatin capsules that do not conform to dissolution specification, *USP* <711> suggests that the test is repeated with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 mL to the medium that has a pH of less than 6.8 (5). Therefore, another six capsules from the original three-month 40 °C and 75% RH storage were tested using the initial Tier II method with premixed medium containing 900 mL of 0.01 N HCl, 1.0% SLS and 750,000 units/L purified pepsin in each vessel. The medium was freshly prepared. The results are provided in Table III. On visual observation, the capsule disintegrated slowly. Some capsules appeared to be gelling with blend trapped inside during the test until a high paddle speed of 250 rpm at "infinity" mechanically ruptured them. The dissolution was slow; the results did not conform to a *Q* value of 70% at 45 min and displayed high standard deviations. In this case, the presence of SLS may have deactivated pepsin as reported.

To remove the effect of SLS on capsule shell disintegration, Medium #1

Table II: Dissolution result comparison of different capsule samples.

	% Release					
	Time Point	Mean (n = 6)	SD	% RSD	Minimum	Maximum
Aged blend in fresh capsule shells	10 min	58.5	2.9	4.9	56.0	62.5
	20 min	74.8	2.8	3.7	71.2	78.6
	30 min	82.2	3.5	4.2	78.5	87.5
	45 min	87.8	3.5	4.0	83.8	93.1
	60 min	91.1	2.8	3.1	88.2	95.5
	Infinity	95.1	1.2	1.3	93.3	96.6
Fresh blend in aged capsule shells	10 min	42.6	29.7	69.7	3.7	75.9
	20 min	69.1	17.3	25.1	45.6	87.2
	30 min	75.5	17.0	22.5	51.1	93.4
	45 min	79.4	16.8	21.2	54.0	98.3
	60 min	86.4	10.8	12.5	68.2	100.2
	Infinity	100.5	2.5	2.5	98.3	103.6
Fresh blend in fresh capsule shells	10 min	70.6	1.2	1.7	69.3	72.7
	20 min	84.2	0.9	1.1	83.0	85.4
	30 min	89.0	1.4	1.5	87.5	90.7
	45 min	92.1	1.9	2.0	89.1	94.4
	60 min	94.8	1.6	1.6	92.8	96.4
	Infinity	99.9	1.5	1.5	97.8	102.0

SD is standard deviation. RSD is relative standard deviation.

Table III: Dissolution results of coaddition of pepsin and SLS in the medium.

Co-addition of pepsin and SLS	Dissolution release (% LC)					
	10 min	20 min	30 min	45 min	60 min	75 min
Capsule #1	31.3	57.3	69.1	77.6	83.7	101.4
Capsule #2	39.6	73.4	85.8	93.8	97.9	101.1
Capsule #3	10.8	38.8	55.5	74.2	85.8	98.8
Capsule #4	44.9	61.8	69.6	77.4	81.7	96.3
Capsule #5	28.2	47.8	57.3	64.2	69.1	94.7
Capsule #6	23.0	38.9	51.0	60.8	66.2	93.4
%Mean (n = 6)	29.6	53.0	64.7	74.7	80.7	97.6
Min (%)	10.8	38.8	51.0	60.8	66.2	93.4
Max (%)	44.9	73.4	85.8	93.8	97.9	101.4
SD	12.1	13.7	12.8	11.7	11.6	3.3
%RSD	41.0	25.9	19.7	15.7	14.4	3.4

SLS is sodium lauryl sulfate. SD is standard deviation. RSD is relative standard deviation.

was prepared consisting of 0.01 N HCL with 750,000 units/L pepsin without the addition of SLS. Tier II dissolution was performed with 600 mL of Medium #1/vessel. Two minutes into the run, all six capsules were observed to be fully disintegrated. At 5 min, 300 mL of prewarmed Medium # 2, consisting of 0.01 N HCL with 3% SLS, was transferred into each running vessel without disturbing the dissolution run. The final composition of the resulting total medium was 0.01 N HCL with 1% SLS and 500,000 units/L pepsin. The dissolution results and profiles are provided in Table IV and Figure 2, respectively. Satisfactory results were obtained, with tight standard deviations.

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Table IV: Dissolution results of stepwise addition of pepsin and SLS in the medium.

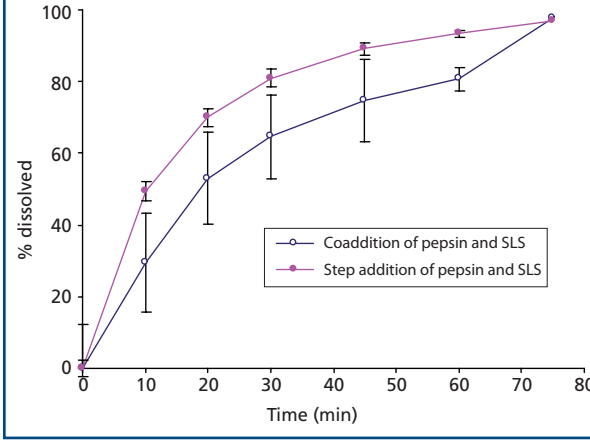
Stepwise addition of pepsin and SLS	Dissolution release (% LC)					
	10 min	20 min	30 min	45 min	60 min	75 min
Capsule #1	51.2	70.5	81.5	88.5	92.6	96.5
Capsule #2	46.3	66.5	78.7	88.0	92.3	96.8
Capsule #3	46.7	67.3	77.6	85.8	92.0	96.4
Capsule #4	49.3	72.1	82.6	90.6	94.3	97.2
Capsule #5	51.4	73.3	84.7	92.8	96.4	98.9
Capsule #6	52.0	70.6	80.8	88.9	92.4	96.4
%Mean (n = 6)	49.5	70.0	81.0	89.1	93.3	97.0
Min (%)	46.3	66.5	77.6	85.8	92.0	96.4
Max (%)	52.0	73.3	84.7	92.8	96.4	98.9
SD	2.5	2.7	2.6	2.4	1.7	1.0
%RSD	5.0	3.8	3.2	2.7	1.8	1.0

SLS is sodium lauryl sulfate. RSD is relative standard deviation.

The results indicated that stepwise addition of pepsin and SLS enabled both agents to take effect individually and sequentially in the dissolution medium. Pepsin digested the cross-linked capsule shells at the beginning, whereas the addition of SLS afterwards increased drug solubility and wettability. Therefore, the addition of SLS to the dissolution medium need not be discouraged when developing dissolution methods for capsule formulations. SLS is commonly included as a wetting agent inside the capsule formulation; this practice should not be affected by the results of this study, because SLS deactivation of pepsin was observed outside of the capsule in the dissolution medium before dissolution took place. By taking a stepwise addition approach, once the cross-linked capsule shell ruptures and dissolution starts, SLS inside the formulation will work as expected.

The 5-min time delay between the addition of pepsin and SLS was further confirmed to be sufficient using more severely stressed capsules. The Tier II method was fully validated for linearity, specificity, accuracy, repeatability, intermediate precision, and stability of standard and sample solutions.

Figure 2: Dissolution profile comparison of coaddition and stepwise addition of pepsin and sodium lauryl sulfate (SLS).



Conclusion

Gelatin capsule shell cross-linking is a common problem for a capsule formulation during stress or stability studies at accelerated storage conditions. Switching the stressed capsule shells and blends with fresh ones can easily prove that the shells are the cause of slowed dissolution. SLS deactivates pepsin despite its advantages and wide use as a surfactant. However, stepwise addition of pepsin and SLS respectively enables each agent to take effect separately. Therefore, SLS need not be abandoned during dissolution method development for gelatin capsule formulations.

Acknowledgment

The authors are grateful to Chris Connolly, manager of analytical development; Jack Chen, supervisor of analytical development; and Andy Cleaver, supervisor of analytical development, for coordinating tasks. We are also grateful to Wendy Liu, chemist in analytical development, for conducting dissolution tests, and Rajeev Bhatnagar, senior technical project lead, for providing fresh capsule blends.

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'Capability of the Art' versus 'Fit for Use'

Clearly Differentiating Three Kinds of Precision

Charles Y. Tan

The US Pharmacopeia draft chapter <1033> "Biological Assay Validation" has made significant progress toward fit for use as a guiding principle for assay validation. However, feedback from FDA at the third USP Bioassay Workshop reveals concern at the lack of criteria for "intermediate precision," and "repeatability," which the draft chapter did not even mention. The author argues that traditional concerns about repeatability and intermediate precision, as enshrined in USP <1225> and ICH Q2(R1), remain valid but insufficient.

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The US Pharmacopeia is replacing its current Chapter <111> "Design and Analysis of Biological Assays" with a suite of five chapters. The draft of Chapter <1033> "Biological Assay Validation" has been published for public comments and clearly takes fit for use as its guiding principle (1). The key breakthrough is that it advocates setting acceptance criteria for precision based on the relative spread of the product versus spread of specification. If a manufacturing process delivers products over a large portion of the specification spread and risks exceeding specification limits, the validation acceptance criteria on precision of the respective bioassay needs to be tightened. Because it uses the process capability index (C_{pk}) for formal assessment this approach is sometimes referred to as the "C_{pk} approach". In this context, the criteria on precision are meant to apply to format variability (variability of the reportable value), which is a new term defined by the following equation:

$$\text{Format Variability} = 100\times\left(e^{\sqrt{\sigma^2_{inter}/k+\sigma^2_{intra}/nk}}-1\right)\%$$

Only when the "specifications have yet to be established" does the draft suggest the application of precision criteria to intermediate precision:

$$\text{Intermediate Precision} = 100\times\left(e^{\sqrt{\sigma^2_{inter}+\sigma^2_{intra}}}-1\right)\%$$

Intermediate precision describes the fundamental variability of the assay, independent of the "use" or "purpose" (i.e., the process and its specification) and replication format. The draft chapter uses geometric standard deviation (GSD), which is also new terminology, in place of the common term of relative standard deviation (RSD). The two are only a reasonable approximation of each other when they are small (less than 20%). GSD and RSD, as well as another closely related metric, are discussed in a previous article (2).

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During the third USP Bioassay Workshop held at USP headquarters on Aug. 11–12, 2010, some chemistry, manufacturing and controls reviewers and statisticians from FDA's centers for drug and biologic evaluation and research provided feedback on this chapter. Their central concerns were basing acceptance criteria on format variability based on the C_{pk} approach, and the complete omission of repeatability in the draft chapter. To make this discussion concrete, repeatability can temporarily be defined by the following equation if using the logic of the draft chapter:

$$\text{Repeatability} = 100\times\left(e^{\sqrt{\sigma^2_{intra}}}-1\right)\%$$

The feedback from members of FDA referred repeatedlyto ICH guidelines and its traditional approach of setting acceptance criteria on repeatability and intermediate precision. Feedback from some industry sources raised similar concerns and objections.

Capability of the art and fit for use

The trend toward fit for use assay validation in recent years represents a step forward. The C_{pk} approach is a clear attempt to put fit for use philosophy into practice. However, there is something to be said about regulators' desire to see repeatability and intermediate precision calculated, and to apply acceptance criteria to them. It is because these two quantities are independent of the intended use or purpose and replication format that they give regulators a chance to assess whether the basic bioassay is optimized for capability of the art.

Repeatability and intermediate precision are related to the standard deviation of individual (relative potency) determinations, not the standard error of averages. With increasing number of individual (relative potency) determinations, calculated repeatability and intermediate precision should converge to the truth, not diminish to zero. They reflect the fundamental variability of the biochemical reaction and readout platform, which can be improved only through assay optimization. However, there is a natural limit because of the underlying biochemistry and technology.

The capability of the measurement procedure and that of the manufacturing process are two independent factors. The intended use of the bioassay often requires much tighter precision than repeatability and intermediate precision suggest. Once it is demonstrated that the basic bioassay has attained capability of the art through repeatability and intermediate precision, manufacturers should be free to design the replication format of the reportable value to take advantage of the power of averaging. Decisions on product quality are made only on the basis of reportable value, not individual determinations.

A compromise between the two doctrines may represent the right path forward: apply acceptance criteria on repeatability and intermediate precision to verify that the basic bioassay has attained the capability of the art, then apply acceptance criteria to format variability to verify that the chosen replication format is fit for use. The goal is to encourage manufacturers to optimize the bioassay as far as technology permits, then allow replication to further improve the bioassay for its intended "use" or "purpose". This approach eliminates unoptimized bioassays where precision is improved only through brute force replication.

Three kinds of precision

Though the current draft Chapter <1033> introduces additional precision terminology, such as format variability, it fails to clearly differentiate different precision types. For example, in Section 2.4 (Validation Strategies for Bioassay Performance Characteristics), intermediate precision is contrasted with format variability as being the one that is independent of replication format; however, in Section 2.5 "Validation Target Acceptance Criteria", σ^2_{RA} is described as intermediate precision when it appears before the C_{pk} formula, but is also described as "(with associated format)" when it appears after the C_{pk} formula.

Three useful species of precision can and should be defined; all of them can be expressed as GSD, following the draft chapter, or RSD, the more common practice. Let σ^2 denote any kind of variance on the natural log scale (of the relative potency), then:

$$\text{GSD} = 100\times\left(e^{\sqrt{\sigma^2}}-1\right)\%$$

$$\text{RSD} = 100\times\left(\sqrt{e^{\sigma^2}-1}\right)\%$$

The three kinds of precision are: source specific precision components; format-independent cumulative precisions; format dependent uncertainty of reportable values.

If σ^2_w and σ^2_b denote within run and between run variance on the natural log scale, respectively, then the source specific precision components are expressed in the following equations.

$$\text{Within run GSD} = 100\times\left(e^{\sqrt{\sigma^2_w}}-1\right)\%\text{, and}$$

$$\text{Between run GSD} = 100\times\left(e^{\sqrt{\sigma^2_b}}-1\right)\%;$$

$$\text{Within run RSD} = 100\times\left(\sqrt{e^{\sigma^2_w}-1}\right)\%\text{, and}$$

$$\text{Between run RSD} = 100\times\left(\sqrt{e^{\sigma^2_b}-1}\right)\%.$$

The between run component can either be larger or smaller than the within run component. In fact, the relative magnitude of the two informs the choice of the efficient replication format.

The traditional concepts of repeatability and intermediate precision, which are format-independent cumulative precisions, are expressed in the following equations.

$$\text{Repeatability GSD} = 100\times\left(e^{\sqrt{\sigma^2_w}}-1\right)\%\text{, and}$$

$$\text{Intermediate Precision GSD} = 100\times\left(e^{\sqrt{\sigma^2_w+\sigma^2_b}}-1\right)\%;$$

$$\text{Repeatability RSD} = 100\times\left(\sqrt{e^{\sigma_w^2}-1}\right)\%, \text{ and}$$

$$\text{Intermediate Precision RSD} = 100\times\left(\sqrt{e^{\sigma_w^2+\sigma_b^2}-1}\right)\%.$$

Because of its cumulative nature, intermediate precision is always larger than repeatability. These two quantities describe the fundamental short- and medium-term variability independent of the replication format. They are useful metrics to evaluate whether the assay has attained its capability of the art via careful development and optimization.

The format variability introduced in the draft chapter describes the variability of the reportable value under a given replication format (*k* within run replicates and *n* replicate runs):

$$\text{Format Variability GSD} = 100\times\left(e^{\sqrt{\sigma_w^2/k+\sigma_b^2/nk}}-1\right)\%;$$

$$\text{Format Variability RSD} = 100\times\left(\sqrt{e^{\sigma_w^2/k+\sigma_b^2/nk}-1}\right)\%$$

It is closely related to ISO VIM3's definition of "Type A (statistical) uncertainty" (3). It is analogous to the standard error of an average, not standard deviation of individuals. It is not fundamental variability but predicted variability derived from experimentally determined components, and can be manipulated via replication format. However, this is the precision that speaks to the variability or uncertainty of the reportable value directly. Because decisions are made based on reportable value, it is the link to fit for use.

Given that there are so many different kinds of precision, sentences, such as "a bioassay with %GSD between 2% and 20%," are too vague to be useful and should be avoided.

Conclusion

Both capability of the art and fit for use concepts are relevant to assay validation. By setting capability of the art acceptance criteria on repeatability and intermediate precision, proper assay development and optimization can be ensured. By setting fit for use acceptance criteria on format variability, reportable values with sufficient quality to support our intended use are ensured.

When specifications are determined by clinical information, say potency specifications based on efficacy and safety, the fit for use acceptance criteria could be established by comparing the specifications to the process variability (i.e., the C_{pk} approach in the draft chapter). However, many specifications are determined based on process consistency (i.e., historical process capability). In this context, the C_{pk} approach is no longer appropriate; the fit for use acceptance criteria need to be established by other means.

Fit for use acceptance criteria are likely to be highly specific to each product's clinical profile and manufacturing process. capability of the art acceptance criteria, however, could be established by proper categorization and an industry norm survey, for which USP is particularly well suited.

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Pharmaceutical Excipients for Hot-Melt Extrusion

Matthias Karl, Dejan Djuric, and Karl Kolter

Various physicochemical characteristics of pure polymers and polymer-plasticizer combinations affect the hot-melt extrusion process. The authors examine the influence of glass-transition temperature, melt viscosity, degradation temperature, and process settings on the process and its resulting extrudates.

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Hot-melt extrusion (HME) technology is prominent in the pharmaceutical industry. Of particular interest is the use of HME to disperse active pharmaceutical ingredients (APIs) in a matrix at the molecular level, thus forming solid solutions. This method is becoming more and more important because the percentage of poorly soluble new chemical entities in drug development is constantly increasing (1). Especially for BCS class II compounds, improved absorption and therapeutic efficacy can be realized by enhancing API solubility (2). An additional benefit of the HME technique is that it is a robust and continuous manufacturing process that can be run in practically any pharmaceutical plant.

However, as with other innovations, numerous obstacles have to be overcome before the technology and resulting dosage forms can be exploited commercially. Compared with other pharmaceutical technologies, such as granulation and compression, hot-melt extrusion is still an emerging method, and its potential has not been explored fully yet. The technology itself can be described as a process in which a material melts or softens under elevated temperature and pressure and is forced through an orifice by screws. Appropriate thermoplastic behavior is a prerequisite of any polymer to be used in hot-melt extrusion. However, the number of such polymers approved for pharmaceutical use is limited.

Purposes of HME

Within the pharmaceutical industry, HME has been used for the following purposes:

- To increase the drug's dissolution rate and bioavailability
- To control or modulate drug release
- To mask the drug's taste
- To stabilize the API
- To create parenteral depots and topical delivery systems.

Personnel can increase the dissolution rate and bioavailability of poorly soluble APIs through HME by forming a solid solution (i.e., solid dispersion) of a drug within hydrophilic excipients. The solid solution is the ideal type of solid dispersions for increasing drug release. In such a matrix, the drug is molecularly dissolved and has a lower thermodynamic barrier for dissolution compared with solid dispersions with crystalline drugs (see Figure 1) (3). Extruded

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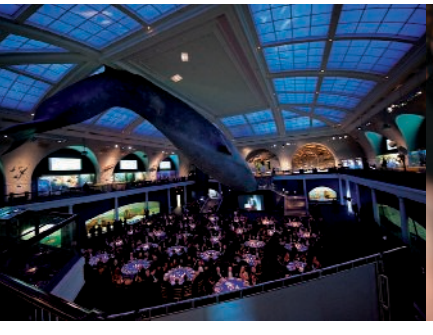

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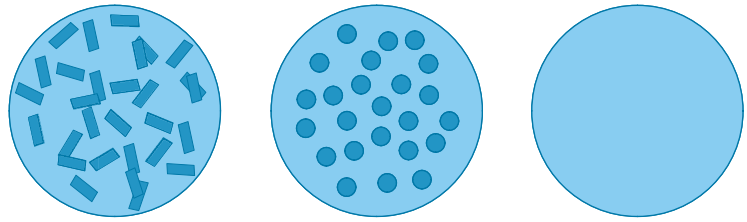
Figure 1: Relevant types of solid dispersions.



	Crystalline	Amorphous	Molecularly dissolved
Drug			
Polymer	Amorphous	Amorphous	Amorphous
Thermo-dynamic stability	Almost stable	Unstable (kinetically controlled)	Stable (drug below saturation solubility)

solid solutions offer higher thermodynamic stability than those prepared by alternative processes, such as spray drying, solvent evaporation, and other hot-melt methods (4).

In comparison with other possible processes, HME is, by far, less complex and more cost effective because its manufacturing process requires only a few steps. HME presents the following advantages over solvent-based processes:

- It eliminates the need to handle explosive solvents
- It does not produce residual solvents
- It enables continuous processing
- It entails few process steps
- It yields high product density
- It produces nondusty pellets
- It is a water-free process
- It can be accomplished through small-scale equipment
- It requires a low investment in equipment.

Furthermore, the polymeric components used in the extrusion process may function as thermal binders, drug stabilizers, drug solubilizers or drug-release controlling excipients.

The choice of an adequate polymer as a matrix to form stable solid solutions is crucial in HME. Polymers with a high solubilization capacity are particularly suitable because they can dissolve large quantities of drugs. Some features, such as lipophilicity, hydrogen-bonding acceptors, or donors and amide groups, are basic prerequisites for a high solubilization capacity (5). This factor explains why povidone, copovidone, and PEG-VCap-VAc are highly suitable for HME. Copovidone and PEG-VCap-VAc, in particular, are more lipophilic than many other water-soluble polymers containing hydroxyl groups. Therefore, they are best suited to the lipophilicity of poorly soluble drugs (6, 7).

When the drug is incorporated in a supersaturated form, the whole mixture should have a rigid structure to minimize crystallization from the dissolved drug and from amorphous drug particles (8, 9). As a solid solution, the formulation dissolves in gastric or intestinal fluids, thus forming a supersaturated solution of the drug and enhancing dissolution and bioavailability (10).

In extruded drug-delivery systems, the polymer serves as a matrix. Larger quantities of polymer thus are required than when the polymer is used as a binder or coating agent. Consequently, it is crucial that the polymers be nontoxic and approved in various countries at high doses.

Experimental methods

Materials. The authors studied copovidone (Kollidon VA 64), polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus; abbr.: PEG-VCap-VAc), povidone grades (Kollidon 12 PF, Kollidon 17 PF, Kollidon 30, and Kollidon 90 F), polyvinyl acetate–povidone (Kollidon SR; abbr.: PVAc+PVP), methacrylic acid–ethacrylate copolymer 1:1 (Kollicoat MAE 100P; abbr.: MA–EA), macrogol polyvinyl alcohol grafted copolymer (Kollicoat IR; abbr.: PEG–VA), macrogol polyvinyl alcohol grafted copolymer + poly(vinyl alcohol) (Kollicoat Protect; abbr.: PEG–VA+PVA), poloxamer 407 (Lutrol F 127 and Lμtrol micro 127). Poloxamer 188 (Lutrol F 68 and Lμtrol micro 68), macrogolglycerol hydroxystearate 40 (Cremophor RH 40; abbr.: MGHS 40), and PEG 1500 (Pluriol E 1500 Powder K) were used as plasticizers. BASF supplied all materials.

Extrusion. Melt extrusion was performed using a twin-screw extruder (ZSK 25, Coperion Werner & Pfleiderer) with a screw diameter of 25 mm and a length-to-diameter ratio of 34. Extrusion parameters included throughput from 2.5 to 5 kg/h, extrusion temperatures of 60–200 °C and screw speed from 100 to 150 rpm.

Film casting. The polymer and plasticizer were dissolved in water. The solution was cast (Coatmaster, Erichsen Testing Equipment) using scrapers with different die gaps of 150–500 μm and dried at 40 °C.

Differential scanning calorimetry (DSC). DSC studies were performed with a Q2000 TA Instruments. DSC scans were recorded at a heating rate of 20 K/min in the second heating run.

Thermo gravimetric analyses (TGA). TGA studies were performed using a Netzsch STA 409 C/CD instrument. TGA scans were recorded at a heating rate of 5 K/min until the ambient temperature reached 450 °C.

General physicochemical characteristics of polymers

Polymers for HME must exhibit appropriate thermoplastic characteristics to enable the HME process, and they must

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BIND Biosciences
Adjunct Professor, University of Wisconsin

Anil Kane, Ph.D, MBA
Senior Director,
Pharmaceutical Technical Affairs—North America
Pharmaceutical Development Services, Patheon Inc.

MODERATOR:

Angie Drakulich
Managing Editor,
Pharmaceutical Technology

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- Hear the direct benefits of achieving bioavailability targets in FTIH Trials for poorly soluble drugs using multiple formulation tools.
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be thermally stable at extrusion temperatures. Other relevant characteristics include a glass-transition or melting temperature (T_g or T_m) of 50–180 °C, low hygroscopicity, and no toxicity (2). The extrudability of a polymer is mainly determined by T_g or T_m and melt viscosity (11). Polymers with a high molecular weight exhibit high melt viscosity and are difficult to extrude. Moreover, a high T_g or T_m requires a high processing temperature that can degrade sensitive APIs (12). As a general rule, an extrusion process should be run at temperatures of 20–40 °C above the T_g. Most polymers demonstrate thixotropic behavior, which means that their viscosity decreases with increasing shear stress.

The glass-transition temperature of povidone homopolymers increases from 90 °C to 156 °C as a function of molecular weight. The relatively low glass-transition temperature of copovidone results from the soft monomer vinyl acetate. The low glass-transition temperature of PEG–VCap–VAc results from the covalently bound PEG moiety. PEG–VCap–VAc therefore can be regarded as an internally plasticized molecule. The PEGs and poloxamers exhibit glass-transition temperatures below 0 °C, therefore the authors give only their melting points.

In principle, all organic materials can be degraded by increasing temperature. TGA is a suitable tool for examining the thermal sensitivity of a polymer. At least at the extrusion temperature, which is usually 100–200 °C, the polymer must be stable. Even if TGA is not capable of delivering detailed information about cross-linking of the polymer chains and other possible reactions, it provides an idea about the changes that take place upon heating. Thus, it enables users to observe changes in mass with increasing temperature and the kind of reactions (i.e., endothermic or exothermic). Personnel also must consider the length of time the material is exposed to the temperature. Long heat exposure might lead to decomposition, although the material might be stable for a short time at the same temperature.

Figure 2: Comparison of the glass-transition temperature (T_g) or melting temperature (T_m) by differential scanning calorimetry with the temperature of degradation (T_{deg}) by thermo gravimetric analyses of pure polymers.

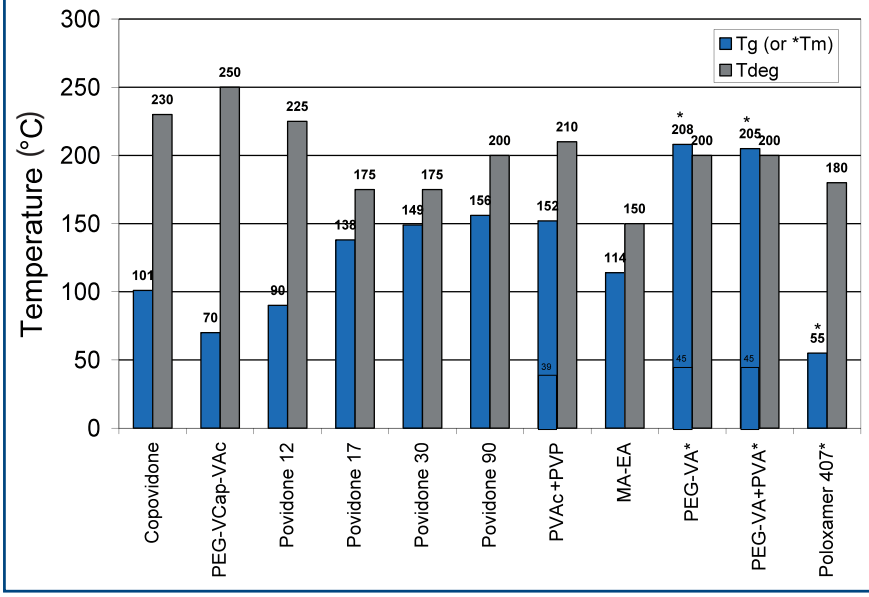
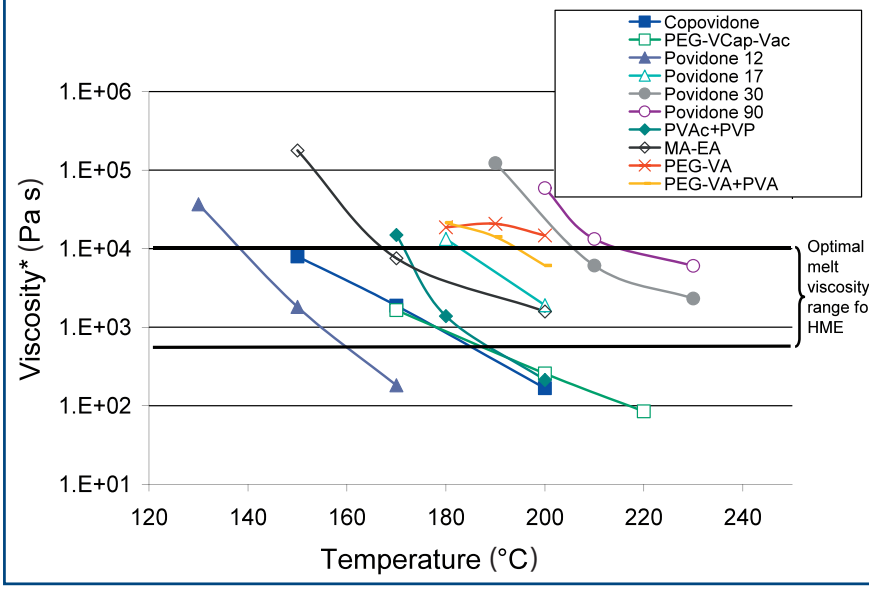


Figure 3: Melt viscosity of pure polymers as a function of temperature.



T_g or T_m and temperature of degradation (T_{deg}) measured by TGA indicate the range within which the extrusion can be performed, from a processability and stability point of view. The broadest processing range can be found with PEG–VCap–VAc, followed by copovidone and povidone 12 (see Figure 2). A large range between T_g (T_m) and T_{deg} is highly beneficial because it offers great freedom for the development of the extrusion process and also serves as a prerequisite for a reliable and reproducible formulation.

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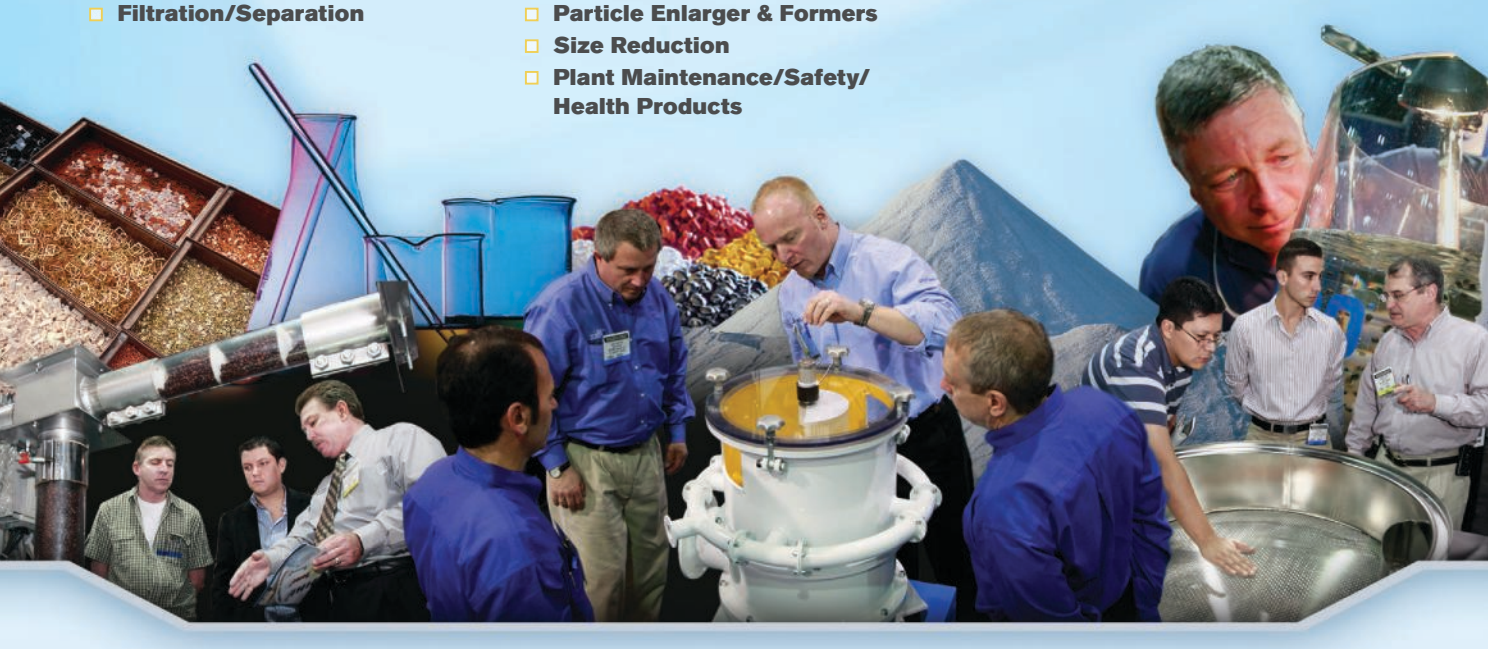

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Figure 4: Glass-transition temperature (T_g) of pure polymers in comparison with polymer–plasticizer combinations (extrudate, 9:1, w/w%).

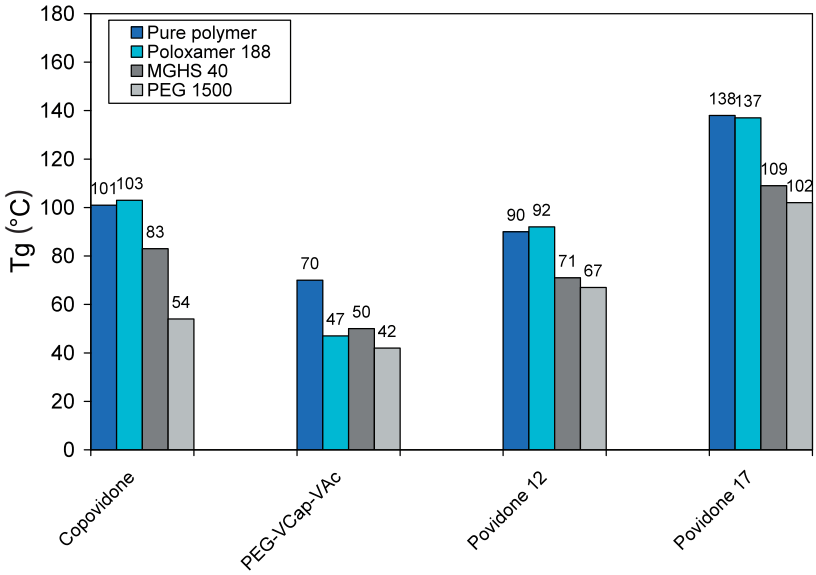
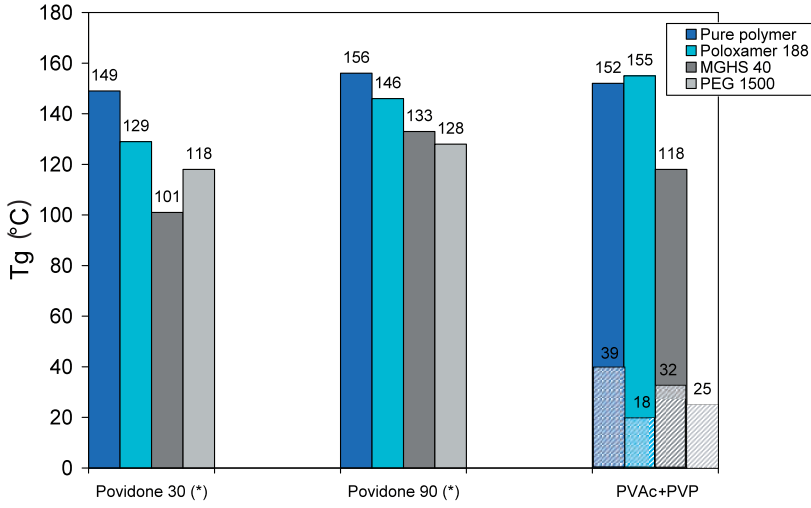


Figure 5: Glass-transition temperature (T_g) of pure polymers in comparison with polymer–plasticizer combinations [extrudate and film (*), 9:1, w/w%], another color in the bar represents the presence of second T_g.



As temperature increased, the dynamic viscosity of all tested polymers decreased. Only PEG–VA showed a slightly higher viscosity at 190 °C compared with its viscosity at 180 °C. This result probably can be explained by the cross-linking of polymer chains. All the values presented in Figure 3 were determined at 16 rad/s.

Melt viscosity is influenced by molecular weight and interactions between the functional groups of the polymer chains. The authors found significant differences between the various polymers. Melt viscosity increased strongly from povidone 12 (~2500 Da) to povidone 17 (~9000 Da), povidone 30 (~50,000 Da), and povidone 90 (1,250,000 Da). Despite a high molecular weight, PEG–VCap–VAc (118,000 Da) results in a similar viscosity to that of copovidone (~55,000 Da). For a small-scale extruder, the limitation is at approximately 10,000 Pa*s because higher viscosities generate too much torque. On the other hand, a low-viscosity polymer could cause problems for downstream processing.

Physicochemical characteristics of polymer–plasticizer combinations

T_g can be reduced by adding plasticizers. An investigation on polymers used in combination with poloxamer 188, MGHS 40, and PEG 1500 was performed to observe the influence of these plasticizers on T_g, temperature range of polymers for extrusion, and melt viscosity (see Figures 4 and 5).

The additives tested acted in different ways. PEG 1500 and MGHS 40 decreased T_g in all systems significantly, but poloxamer 188 had no effect on several polymers. From these results, it can be concluded that PEG 1500 and MGHS 40 dissolve more homogeneously in most of the polymers tested than poloxamer 188 does. This result can be related to the higher molecular weight of the poloxamer.

Processability

Taking the T_g or T_m, the melt viscosity, the T_{deg}, and the determination of the lowest and highest processing temperatures by HME into consideration, the pure polymers copovidone, PEG-VCap-VAc, povidone 12, and poloxamer 407 demonstrated excellent suitability for extrusion (see Figure 6). Povidone 17, PVAc+PVP, PEG–VA, and PEG–VA + PVA were difficult to extrude because of their high T_g or T_m, melt viscosities, and the small difference between T_{deg} and T_g. PVPs of higher molecular weight (povidone 30 and povidone 90) and MA-EA as pure polymers were not processed by HME because of their degradation.

Three plasticizers (poloxamer 188, MGHS 40, and PEG 1500) were investigated in combination with these polymers. In general, 10 % (w/w) of the plasticizers was sufficient to decrease extrusion temperatures significantly (see Figure 6).

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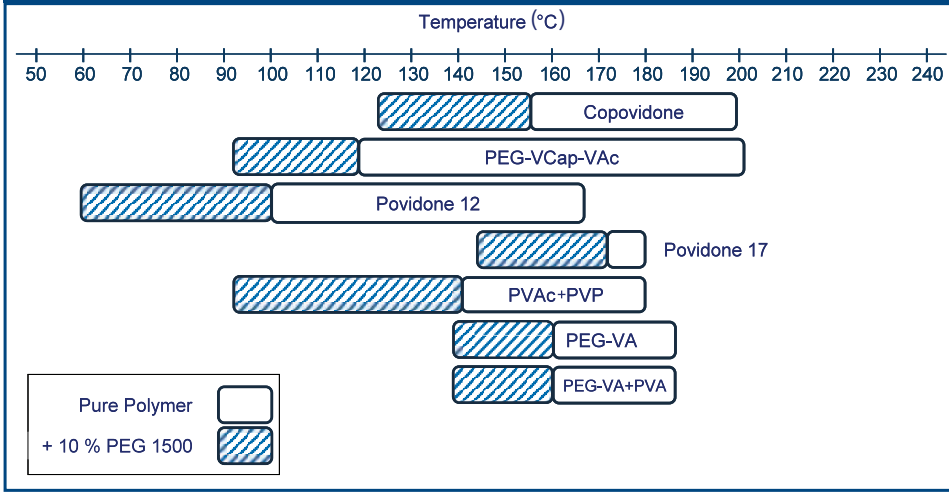
Poloxamer 188 and PEG 1500 could be added in powder form using a separate powder feeder. MGHS 40 was added in molten form using a melt pump. The temperature range for extrusion was determined according to the method employed for the pure polymers.

All the polymer–plasticizer combinations could be processed below the processing temperatures of the pure polymers. However, this reduction in temperature was not the same for all polymers. The highest reduction of 50 °C was observed for PVAc+PVP with all three plasticizers. This result is consistent with previous studies on the plasticizing effects in film coatings based on polyvinyl acetate, where small amounts also showed a tremendous effect.

The type of plasticizer also had a significant effect; PEG 1500 decreased the extrusion temperatures more than the other plasticizers. This result probably can be attributed to the low molecular weight of this plasticizer.

Figure 6: Temperature range of polymers and PEG 1500 combinations for extrusion (9:1, w/w%).



Conclusion

Suitable T_g (T_m), T_{deg}, and melt viscosity are relevant physicochemical parameters of the polymer in HME. A large range between T_g (T_m) and T_{deg} of the polymer is highly beneficial because it offers freedom for developing the extrusion process. PEG–VCap–VAc is characterized by the widest temperature range for extrusion, followed by povidone 12, and copovidone.

The type of plasticizer has a major influence on T_g, melt viscosity, and the temperature range of the polymer in the HME process. A plasticizer principally enables extrusion processes to occur at low temperatures.

The knowledge of polymer and plasticizer characteristics and their effects on the extrusion process and resulting extrudates is an important prerequisite for the quick and successful development of an extruded drug-delivery system.

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What would you do differently? Email your thoughts about this paper to ptweb@advanstar.com and we may post them on PharmTech.com.

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How to Optimize Outsourcing CMC Development and Manufacturing

Gregg Brandyberry, CEO of Wildfire Commerce and senior advisor for A.T. Kearney's Procurement and Analytic Solutions

Clive Bennett, non-executive chairman of Halo Pharmaceutical

George Bobotas, chief scientific officer of Halo Pharmaceutical and managing partner at DeMelle BioPharma

Industry experts offer practical advice on the commercial and technical considerations in CMC outsourcing

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In today's environment of increased pressures to speed time to market and constrained internal resources, pharmaceutical companies are turning to external partners to meet their strategic business goals. Three leading experts explain how to optimize the outsourced relationship between a sponsor company and a contract development and manufacturing organization (CDMO) and contract manufacturing organization (CMO) by offering practical advice on those external partnerships in development and manufacturing.

Gregg Brandyberry, CEO of Wildfire Commerce and senior advisor for A.T. Kearney's Procurement and Analytic Solutions, and former vice-president of procurement of global systems and operations at GlaxoSmithKline, offers a Big Pharma perspective on CDMO and CMO selection. Clive Bennett, non-executive chairman of Halo Pharmaceutical, provides commercial considerations when outsourcing dosage-form development and manufacturing. George Bobotas, chief scientific officer at Halo Pharmaceutical and managing partner at DeMelle BioPharma, discusses the technical considerations when outsourcing. A recorded webcast of this panel can be found at http://pharmtech.com/cmc.

Sponsor Company Expectations and CDMO and CMO Selection

Gregg Brandyberry, CEO of Wildfire Commerce and senior advisor at A.T. Kearney's procurement and analytic organization, and former vice-president of procurement of global systems and operations at GlaxoSmithKline

There's never been a better time than today for all types of CMOs. This is being driven in part by the fundamental changes that have been occurring during the past 10 years among the giant pharmaceutical companies. Big Pharma has had to react to myriad cost pressures, driven by a multitude of issues, including more costly development cycles with fewer successes, much tighter regulatory control, global governmental price controls, and legislation favoring generics. Because of these pressures, we've seen continued mergers and acquisitions,

which has driven major manufacturing network rationalization with a greater tendency for Big Pharma to look externally at CMOs to aid in all stages of product development and ongoing manufacturing. And there's also a proven business case. Why keep costly assets, both in people and capital on the book, when they can be readily available externally from all over the world. The availability of highly qualified third parties is growing and becoming more competitive as a supply market.

As Big Pharma has fundamentally changed, contract manufacturing opportunities have grown. Years ago, CMOs were typically used for secondary packaging. We began to see the growth of CMOs involved in primary packaging of all types, including tablet packs, liquid fills, blister packs, and a host of other packaging configurations. For Big Pharma companies that had diversified with consumer products and with over-the-counter switches, contract manufacturers became popular for the full manufacturing process, even including capabilities such as flavor development. As CMOs became highly sophisticated, Big Pharma has turned to them for increasing complex activities, such as active pharmaceutical ingredient (API) development and manufacturing. Today, we are seeing chemistry, manufacturing,and controls (CMC) CMOs heavily involved in new chemical identity development and trialing and all the way through to off-patent product manufacturing.

Successful buyer–seller relationships with CMC-CMOs are based on rigorous health and safety regulations, specifications, and sophisticated materials and technologies.

Collaborative Optimization

Picking the right CMO, whose philosophy is aligned with your own company, therefore, is absolutely crucial. Optimizing the right mix of CMOs to cover your organization's needs can be complex. The existing network is typically the result of mergers, acquisitions, co-marketing deals, and other arrangements. This often results in a difficult and inefficient network to manage. The latest best practice that I've been involved with, to develop the best possible solution for complex spend areas, is called collaborative optimization, a powerful procurement process when you have many specifications, many potential suppliers with multiple capabilities, and regional or global supply lines. It consists of three major components and is designed to rationalize and optimize a spend category or multiple spend categories to a single procurement initiative.

The approach of collaborative optimization allows for a deep cost analysis of all labor, materials, technology, and any other factor that is part of the overall cost makeup of a product. It provides suppliers, in this case CMOs, with the ability to bid on what is not only being requested, but also to bid creatively, that is, give input to more cost-effective solutions, which is called expressive bidding. The huge amount of data from all CMOs participating can be very quickly analyzed using combinatorial optimization, thereby allowing very quick analysis of what-if scenarios to determine the lowest total cost network or perhaps the best total cost network that include certain must-have requirements. What I like best about this approach is that it does not pit supplier against supplier, but determines the best overall network where everyone benefits mutually.

The most critical CMO relationship is one involving chemistry, manufacturing, and controls. Successful buyer–seller relationships with CMC-CMOs are based on rigorous specifications, health and safety regulations, and sophisticated materials and technologies. These relationships involve taking small laboratory quantities to large production batches, considerations for protecting intellectual property, and complex contracts involving sophisticated payment schemes, including toll manufacturing, cash/flow strategies, tiered-volume pricing, gains/share schemes, and even royalty payments in certain types of relationships.

Supplier Relationship Management and Beyond

It is obvious that these relationships and resulting contracts need skilled technical, legal, and, of course, procurement representation. To manage a network effectively, Big Pharma typically puts in place a supplier relationship management (SRM) program. Beyond SRM, the really good Big Pharma procurement organizations also facilitate an ongoing process that helps to drive supply-chain innovation by working collaboratively with the CMOs to unlock new sources of value that can benefit both parties. SRM is designed to ensure that the contract terms and conditions are followed and yield the desired results.

SRM also involves making sure that contracted service level agreements (SLAs) are in place and delivered upon. SLAs are typically a combination of specification-driven and service-quality and supply-related requirements. These are tracked and reported. Typically failure to perform them will result in an official notice of nonperformance with a request for remedy by a specified time. SRM also includes periodic supplier reviews, where both parties can review past performance and plan future activities. A scorecard is typically presented, which looks at the salient metrics of the overall relationship. SRM also becomes the activity that leads to agreement on joint efforts to reduce costs from any other types of improvements.

Creating new streams of value from existing relationships requires creating a future vision. Goals should include the desire to enhance the mutual success of both the buying and supplying organizations, and, most importantly, creating the collaborative environment that increases the latency of both organizations. This untapped potential will take the shape of higher organizational energy, and much more ingenuity on the part of all participants, thereby resulting in increased profitability for both the buying and selling organization.

Some say that the complexity of manufacturing, marketing,

and distributing globally outweighs Big Pharma's ability to provide adequate controls, which might lead to major failure. I would counter this by saying that with the selection of the right CMO network, putting in place the right programs, the right operating philosophy, and the commitment for producing quality products with cost-effective pricing, Big Pharma will succeed and prosper within the ever-changing and challenging global marketplace.

Halo Pharmaceutical's Clive Bennett on commercial considerations in outsourcing

Commercial Considerations in Outsourcing

Clive Bennett, non-executive chairman of Halo Pharmaceutical

I would like to provide some practical advice and to offer several practical points I have learned from my Big Pharma experience [nearly 25 years], but mostly from the last nine years that I've spent as part of the contractor community. There's a huge range of effort that companies put into transmitting the information that a CDMO needs to do for a decent job of drawing a proposal, let alone carrying out the technical work itself. Similarly, the amount of energy different companies put into choosing the right contract varies a great deal. Virtual and emerging biotech, mid-sized specialty companies, and Big Pharma differ a very great deal in the amount of resources they can have. It's not unusual to find consultants acting as intermediaries between the client and the CDMO, particularly in the case of smaller client companies. Managing this three-way interaction can be a challenge and needs to be thought through properly. Lastly, I'll discuss the negotiation and management of the various agreements that are intrinsic to these relationships, and the key metrics that are needed to track the development or commercial manufacturing relationships. My advice will be directed to the client company rather than the CDMO.

Timing

In a situation where both the development and manufacturing work for a successful product will be conducted at a CDMO, the vast majority of the value for the CDMO, and the majority of the expenditure by the client company, lies in commercial manufacturing, which will typically be governed by a manufacturing supply agreement (MSA). My first advice is that it's absolutely essential that the MSA start to be negotiated when the product enters Phase II. It may not be possible to conclude all the legal language in the MSA this early, but formal and binding heads of agreement, including a then-current estimate of commercial price per unit, really do need to be established at this time.

As development proceeds, there should be provisions for revisiting the heads of agreement and refining the terms, including, if necessary, price, which could move in either direction, depending on additional information about the processing and the yields. It's well-known by the CDMO and client alike that no pharmaceutical company wants to move a product between the beginning of Phase III and commercial launch. Leaving negotiation of the MSA terms later than early Phase II really puts too much leverage into the hands of the CDMO, no matter how good the relationship between the parties.

Separation of Development and Manufacturing

Organizational separation of development and manufacturing is the norm in the pharmaceutical industry. This separation causes distinct problems for the development and launch of products, such as difficulties during scale-up and transfer to the commercial facility. The objectives of development, which typically are to get to the earliest possible successful product-approval date, and the objectives of manufacturing, which typically are to successfully and reliably manufacture the product long term at a good price without significant waste, are often somewhat in conflict with one another. A decision made by development or manufacturing alone may be a bad decision for the long-term interests of the company owning the intellectual property. For example, choosing a CDMO with good development resources, but questionable manufacturing capabilities for a project that is in Phase II leading into Phase development, does a company a considerable disservice. I would say that from my CDMO experience it is rare for a company to conduct a commercial manufacturing GMP and capabilities audit at the time of award of a Phase II or even Phase III development project. Manufacturing should be involved considerably before the filing of registration, and development should be involved well after commercial launch. Such an approach is rare, but needs to become the norm.

Scopes of Work

Size of scope. Regarding development scopes of work, my advice is to have many smaller scopes of work rather than one scope with a very large amount of work involved. Small scope sizes are manageable and motivate the CDMO in the hope of securing future business. It's in the nature of pharmaceutical development work that there are discoveries that change the work involved as more and more is known about the molecule and the associated dosage form. This means that changes of scope are likely to be needed as work proceeds. It's not reasonable for a client to expect considerably more work to be done for the same price contemplated in an original scope of work. On the other hand, it's not reasonable for a CDMO to expect to be paid extra for every minor nuance of change. A large original scope may lead to many changes in that scope before the work is completed. Far more successful is the modified scope of work, which may generate none or at most one or two mutually agreed changes of scope before it's completed. In any event, at the time of award of any development work, it's important that the client company understands and agrees with the CDMO's policy and procedure for changes of scope to ensure there are no misunderstandings or hard feelings as the work proceeds.

Information and exchange of information. When putting together the scope, be sure to think it through thoroughly and carefully, and as far as possible, describe your expecta-

tions accurately as they apply to analytical development and formulation development. This attention to analytical development applies even if you think you're requesting a technology transfer of a commercial product from one factory to another. It's amazing how quickly regulatory expectations for analytical methods can advance. A technically competent and conscientious CDMO should be telling you where the technology needs to be brought up to date. Such suggestions must be carefully considered. Both parties have a responsibility for GMP. And it's the CDMO that the FDA investigator will first be quizzing about the adequacy of methods once transferred.

For example, it is crucial to provide adequate information about the tablet weight, the process contemplated, or the quantity of tablets required. It does not cost the same to make an uncoated, directly compressed tablet as it does to make a wet-granulated, spray-dried, and solvent-film coated one. Requests without precise information are really non-questions. Put considerable thought into what you want and write it down for discussion purposes prior to your first telephone interview with a CDMO. Particularly for products in development, and even in the case of late life-cycle situations, volumes required often are not crystal clear, but estimates are needed to allow the batch and campaign lengths to be established. CDMO price is often very dependent on batch size and run length. Without a volume, a competent CDMO or client company can be put at a commercial disadvantage if a reasonable effort is not made to estimate volume requirements.

When exchanging project information, it is crucial to provide adequate information about the tablet weight, the process, or the quantity of tablets required.

CDMO selection. Your best strategy when choosing the contractor is to approach about half a dozen CDMOs that appear to have the necessary technical ability and which can provide you with a single point of contact with whom to work. Of these six, you'd be wise to sign confidentiality agreements with three to five and get proposals, including price, from at least three after a preliminary visit and rough audit. Discussion with these three will soon tell you which CDMO gives you comfort in order to make your final selection for a full GMP audit, proposal acceptance, and start of work.

Project management. Pay special attention to who the project manager will be and to specifically who will be on the project team. Take time to meet them before signing up for the job. In my experience, problems during any project are just as likely to be caused by problems of personal interaction as they are to be technical issues. Expect your CDMO only to be as reasonable as you are prepared to be. For virtual and emerging biotech, and to some extent for specialty pharma companies, consultants are often used. Remember that the consultant's interests may not be automatically and completely aligned with your own, even though you are the client. So be careful. While you want to get a good, compliant job done quickly, the consultant on the other hand, and this is particularly true if he/she is not the strongest technically, may on occasion be motivated to impress you with how value-added they are. This can often lead to shadow-boxing problems that are not real. Managing a three-way relationship of client, consultant, and CDMO is more complicated than the two-way client–CDMO partnership. Just make sure that everyone in the relationship is essential, strong, technically capable, and value-added.

Big Pharma is now setting up external manufacturing organizations that look like site-management teams with each discipline represented. For large companies, this is a very good approach. Although procurement will often take the lead in an external-manufacturing structure, it also can immediately draw on quality, production, or process-engineering expertise within its team. If looking at a development project, there's an obvious role for the scientist throughout, but there's also an important role, at least in large companies, for the procurement professional, whose focus will be on getting best value for the intellectual property owner's money while the scientist focuses on technical and scientific excellence.

Timelines. Having put energy into precisely defining the scope, this stage is the time to focus on expected timelines for deliverables with the price based on very clear expectations. For example, don't find yourself in a situation where you thought there would be a free engineering batch with associated testing before the registration batch and the CDMO didn't understand that. The parties need to agree on what the milestones are for billing and which have scientific, regulatory, and commercial significance for the client. Find a CDMO with a solid contractual template that will deal with all the standard provisions for the MSA or for the development agreement as applicable. By achieving a tight scope of a size that is unlikely to generate too many changes and with control over any changes of scope that may arise, you have a good start toward managing the timelines.

The CDMO needs to provide a strong project manager, capable from both the technical and human-interactions perspective of driving the project. The development team needs to be able to represent all the technical perspectives from the side of the client as well as from the side or with respect to the CDMO. No later than one year before filing, a representative of the client supply-chain management needs to join the team to handle both procurement and planning perspectives. Project-team meetings need to be frequent and representative of the pace of work. Team meetings should take place not more frequently than once a week and not less frequently than once a month. Work to develop complete openness. Everything is not going to go completely smoothly. The technical issues are generally too complicated for there not to be bumps along the road. But if the team is honest and straightforward with one another, that same team will solve the problems. In this way, trust will develop, and

the group will want to work together again on future projects.

Managing the relationship. If your MSA was well negotiated and technically sound, fairly representing the interests of both parties and the world's realities, you have the basis for managing the supply for the long term. Both parties need to pay attention to their obligations under the agreement. This means that the client must pay attention to the forecasting requirements of the contract in the same way that the CDMO must be diligent about providing deliveries on time. Good CDMOs will do everything they can to respond to a new demand 30 days out, but it may be difficult depending on the component and other lead times. If the MSA says firm 90-day orders, it probably says that for a good reason. If the client company is large, the CDMO should be held to the same performance expectations as the plants in the client's internal plant network. Usually, the CDMO performs as well as or better than the best internal plants.

Make sure that there are quarterly business review meetings between the CDMO and client supply-chain, technical, quality, and commercial personnel. A healthy relationship will develop from quarterly discussion of problems, their resolution, API yields for product manufactured in the quarter, minor product changes, and regulatory inspection results. Don't leave the relationship on autopilot while simultaneously expecting that relationship to arrive in the right place.

And, finally, in the case of commercial manufacturing, there generally are a standard set of key metrics that client companies want to negotiate in the MSA, and they expect CDMOs to measure themselves against these key metrics with oversight from the client's supply chain. These key metrics typically revolve around measures of product quality and regulatory compliance and the extent to which deliveries by line item are on time and represent accurately the volumes ordered and the standard order quantities. From the CDMO's perspective, its metrics are whether the client's accounts-payable department pays in accordance with the payment terms in the MSA and whether the supply-chain organizations are living up to their forecasting expectations. For the development agreement, on-time delivery of milestones is key, as are measures of the quality of data and development reports written by the CDMO. Measurement of communication efforts and the performance of the client's accounts payable department are as important here as they are in the case of commercial agreements.

Halo Pharmaceutical's George Bobotas on technical considerations in outsourcing

Technical Considerations in Outsourcing

George Bobotas, chief scientific officer of Halo Pharmaceutical and a managing partner of DeMelle BioPharma.

Before we look for vendors or create requests for proposal (RFPs), our first steps start with the project. We should first ask ourselves whether this is a development or manufacturing project requiring a contract development and manufacturing alliance or is this really a tech transfer of established manufacturing and analytical technology to be followed by clinical or commercial manufacturing?

Development Projects

For a development project, you should first be sure to gather all available data. It will take a while to obtain the necessary documents. For a commercial manufacturing process, before moving a process, do your own due diligence to anticipate issues. For a product that's still in development, the types of issues to first consider for a new chemical entity (NCE) is sufficient toxicological data for assigning a level of toxicity, which will in turn, guide the level of containment needed from an environmental and safety perspective. Of course, at this time, begin your review of the analytical methodology and the formulation work that's been done. Also, you can't begin your project without the following two considerations: how much API is needed versus how much API is actually available now and how long will it take to get more. Estimate the lead times for other key components and materials, which will be very important in putting together your project timeline.

Tech Transfer and Manufacturing Projects

For a tech transfer and manufacturing project, gather and review available information. As your goal is to facilitate and make this project successful, be familiar with this information, such as batch records, the validation report, and particularly seek out the weak areas in the process. For the purpose of communication, prepare a process-flow chart with specific equipment information. Look into the type and quantity of organic solvents that will have environmental impacts, which may disqualify some CMOs. Find out what your goals are—for example, when do you need to ship product from a newly approved CMO site to commercial networks or into a clinical development program?. Also, how much product do you need, what's your expected quarterly and annual forecast? That will have an impact on your batch size and the design of your campaign.

The Sponsor's Team's Pre-CMO Activities

If you haven't done so before, form an internal team drawing from key areas, such as manufacturing, formulation, quality, analytical, and project management. Working together in a consensus-building manner, construct the project document with background technical data and suitable goals. Facilitate and ask questions, such as what dosage forms and strengths does your clinical marketing group require. Also allow enough time for your marketing group to reach its decisions because sometimes focus groups are needed or other factors are involved. In addition, identify the packaging requirements for both trade and sample packages.

And think about strategies. We're all guided by the regulatory framework within our industry. Is this a new drug application (NDA), an abbreviated new drug application (ANDA). Does SUPAC come into it? Do you need to prepare comparability

protocols? Request a prior written regulatory assessment of any changes. Clinically, will any sites be used in Europe? That will have an impact on your selection of CMOs because some CMOs are not in a position to meet the requirements of the European Medicines Agency. In summary, get buy-in from your regulatory and clinical colleagues.

Selection of a CMO

After you have your team gathered, begin the selection and evaluation of a suitable CMO. You can start by preparing a due-diligence list of questions and required information. This list can be used for more than one product but should be fine-tuned for the needs of the specific project. Prepare an RFP with a suitable description of the process and of the scope of required services. CMOs are not very good at mind-reading. It becomes a costly proposition to have to refine proposals if the information is not accurate. Drawing on past experience, websites, and public information, prepare a list of CMOs to contact. What I have done in the past, is to have a database of vendors and CMOs with their information, which saves time in mobilizing your efforts. Check the GMP status of a CMO using available information and make sure to recheck their current status.

Advice to the sponsor company: Form an internal team from key areas, such as quality, formulation, analytical, manufacturing, and project management.

Initial interviews and assessment. Eliminate, of course, any CMOs with respect to apparent quality issues. This is followed by telephone interviews of candidate firms, approximately six in number. I also like conducting interviews at conferences such as AAPS or Interphex, which is very efficient and save a great deal of time. Request equipment lists with the specific equipment models. If you start changing equipment, as well as site locations, you're going into the realm of multiple changes, which is an area you don't want to enter. It's important to get equipment with the same principles of operation as you currently are using for a site change. Initiate confidential disclosure agreements (CDAs) with candidate firms after eliminating any with a poor fit.

RFP process and facility review. Start with sending an RFP once the CDAs are in place to each remaining CMO. After receiving the proposals, review the proposals with your team, and narrow the list down to two or three firms if possible. Pay attention to the comments of your colleagues, particularly your manufacturing and regulatory colleagues. They have a different perspective that's quite valuable. Schedule on-site meetings for an interview directly with the CMO and also for inspection of the CMO facility. At the site, request to meet with the actual technical team and pay particular attention to the assigned project manager to assess his experience. Tour the facility to get a feeling for where your product will be made. At the meeting, request the tabulation of standard operating procedures (SOPs) and organizational charts, which will be quite useful for any audit team to follow. Discuss the details of the project and evaluate the management team's commitment. If the management team is too busy, that's clearly not a good sign.

Ranking and evaluation. Back at your facility, rank the CMOs and their proposals. Evaluate quality compliance, by audits of the top two candidate firms. At this time, look into the financial evaluation of these firms. It doesn't do any good to have a technically competent firm that won't be around in the future. Finally, schedule a conference call between your internal project team and the relevant project team at each CMO to determine how well they communicate over the phone and to again assess the capabilities of the project manager at each CMO by how each one runs the meeting and facilitates discussion. Once you have the compliance and financial evaluations, write the final evaluations to have a record and to get everyone's attention focused on the selection process. Select the CMO and notify the other CMOs not selected and explain why.

Negotiations and planning. The next steps are to negotiate the service and manufacturing agreements. To facilitate project planning, it's useful to have a letter of intent to allow the sponsor CMO team to begin more specific activities. Schedule a kickoff meeting of the project team and prepare a more complete data package for the CMO that will have the information that they would need to conduct the project. Although this kind of information, analytical and formulation process, is usually available, it's important to organize it and put it into perspective for the CMO. For early-development projects, include as much information as possible because the process is not fixed and may change. To avoid any uncertainty, it's always good to have this information available at the beginning. Finally, communicate and work together as a single team because you both have a single goal. ♦

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Monograph Makeover Requires Industry Input

Karen Russo and Shawn Dressman

Monograph modernization and standards donation go hand in hand.

The cover story of this issue of *Pharmaceutical Technology* is devoted to over-the-counter (OTC) medications—how they're regulated, and what safeguards are in place to help ensure their quality and safety. These complex issues have been in the news quite a bit lately. Consumer confidence has been shaken by multiple recalls of common products. The US Pharmacopeial Convention (USP) plays a specific role in ensuring the quality of OTC drugs by setting standards for drug formulators and manufacturers in the *US Pharmacopeia–National Formulary* (*USP–NF*). The adulteration and misbranding provisions of the 1938 Food, Drug, and Cosmetic Act establish *USP–NF* in US law and are enforceable by FDA.

USP cannot create and update standards—whether written monographs or physical reference materials—without a close partnership with industry as well as FDA. Currently, USP is working on an ambitious project that it started more than a year ago to update key monographs to incorporate modern analytical methods and technologies. FDA has provided valuable guidance to this project by identifying priority monographs, based on exposure to the population and relative risk of quality concerns (e.g., inadvertent contamination or economically motivated adulteration). The Consumer Healthcare Products Association (CHPA) is also collaborating on the project. Most of the priority monographs are used for nonprescription products, although some (e.g., acetaminophen with codine) are prescription as well. CHPA's participation in the effort highlights the unique collaboration taking place in industry to ensure the quality of OTC medications for the marketplace.

FDA Commissioner Margaret Hamburg exressed support for USP's standards modernization project during her remarks at the USP Convention meeting in April 2010. She cited the effort as one of the most pressing tasks facing USP and FDA given the disturbingly frequent incidents of poor-quality products in the OTC and prescription arenas.

The project thus far has involved identifying and prioritizing a master list of existing monograph procedures of interest as candidates for modernization. A list of the top 300 (200 are for drug substances, 100 are for excipients) monographs selected for modernization was posted on the USP website in February 2011. Of the initial list of monograph candidates, about 25% are OTC-related. It is important to note that the same product or ingredient can be OTC, for example, in low doses, and available as a prescription at high doses or in a different dosage form.

USP has begun to seek external (primarily from industry) and internal support (primarily from USP laboratories around the world) for the project. The convention is focusing on: replacing outdated technology and methodology with current procedures; adding critical tests to monographs (e.g., for impurities); and deleting tests that are no longer relevant, such as those for odor or melting point. A primary challenge is obtaining the best procedures and acceptance criteria from the manufacturing community. To address this challenge, USP has launched several outreach programs, including a public webinar.

USP has traditionally relied on donated procedures with supporting documentation from industry as the primary basis for its standards. The proposals are put through USP's rigorous, public, and transparent vetting process, involving many volunteer experts who evaluate the standards and seek input from industry, regulators, and other interested stakeholders. The resulting public standards (as compared with a manufacturer's private specifications, which are a component of the drug-approval process for new drug and biologics license applications) are beneficial to the donor and the public in following ways:

- Public standards level the playing field for buyers and sellers by helping to establish the identity and quality of medicines
- A public standard defines an "article of commerce" and is accessible to everyone
- USP monographs provide a legal standard of quality for the United States and international markets
- USP monographs help ensure product quality across manufacturers, contributing to public confidence in the medicine supply.

By donating a monograph modernization procedure, the donor has a

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Karen Russo, PhD, is vice-president of small molecules, and **Shawn Dressman, PhD**, is vice-president of standards acquisition, both at the US Pharmacopeial Convention (USP), kar@usp.org, sfd@usp.org.

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Supply-Chain Pain

Jim Miller

Lessons from the earthquake in Japan show the vulnerability of the bio/pharma supply-chain.

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PharmTech.com/outsource

The tragic earthquake and tsunami in Japan in March rocketed supply-chain issues to a prominent position. Even the most sophisticated supply-chain managers were caught off guard by the event, which caused the shutdown of many manufacturing sites due to earthquake damage or power-supply interruptions.

What is striking about the impact of the Japan earthquake on the supply-chain is the widespread production disruptions caused by supply interruptions of simple components. Automobile manufacturers were forced to shut down manufacturing operations at plants around the world due to component shortages. For example, Ford halted shipments of some cars just because of a shortage of certain paint pigments. Perhaps most famously, production of Apple's iPad2 was threatened by the shutdown of a supplier in northeastern Japan making a connector costing just a few cents.

The automobile and electronics industries are known for their supply-chain sophistication, including their ability to source components globally and have them delivered just-in-time to the manufacturing floor. The fact that their production would be disrupted by such minor components speaks to just how complex effective supply-chain management really is.

Bio/pharma industry vulnerability

Reports so far suggest that the bio/pharmaceutical supply-chain has only been marginally affected by the events in Japan. We have heard of only two interruptions. One was from a supplier of glycine, an ingredient in some common solid-dosage products, which indicated that production may be shut down for up to 24 months. We also heard of disruptions in some supplies of gelatin used in softgel capsules, for which alternative suppliers are readily available.

Jim Miller is president of PharmSource Information Services, Inc., and publisher of *Bio/Pharmaceutical Outsourcing Report*, tel. 703.383.4903, fax 703.383.4905, info@pharmsource.com, www.pharmsource.com.

Operational excellence in managing the supply chain is of value to CMOs.

Nevertheless, the bio/pharmaceutical industry has not been without its own supply-chain difficulties in recent months. A major fire destroyed a warehouse attached to Catalent's commercial packaging facility in Corby, United Kingdom, and problems stemming from delamination in glass vials resulted in a number of injectable products being recalled from the market.

The pharmaceutical industry has done surprisingly little to protect itself from supply-chain interruptions. PharmSource recently conducted a survey about a widely used component for solid-dosage drugs, which typically requires preformulation compatibility testing, and found that few companies have exhibited the foresight to qualify second or third suppliers.

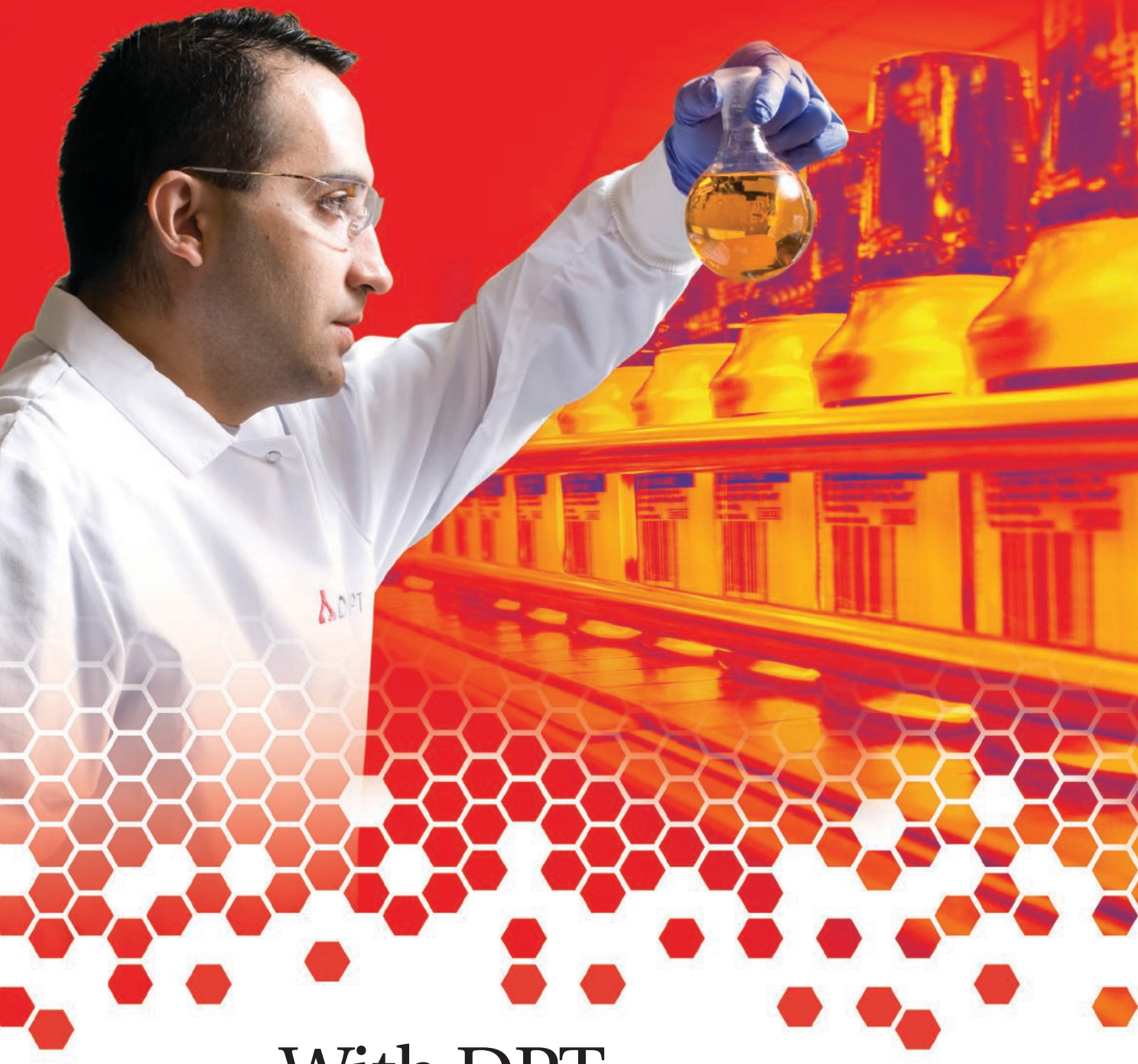
For component-assembly industries, such as automobiles or electronics that are relatively unregulated, the interruption in the supply of a minor component will be disruptive and relatively short-lived. In most cases, it could be a matter of weeks to redesign the component or have substitute suppliers step in for secondary supply. In the bio/pharmaceutical industry, however, the long-term interruption of a minor component could be catastrophic. Even a relatively minor excipient can cause changes in a product's characteristics, thereby requiring full preformulation analysis, stability testing, and testing of production batches. Add to that the supplier qualification and regulatory-filing requirements, and the production time lost can be considerable.

This lack of advanced planning by bio/pharmaceutical companies is surprising because the potential costs are so high. An extended period of lost production means lost sales and loss of market share to competitors that might never be regained.

Inadequate supply-chain practices

The bio/pharmaceutical industry's lack of supply-chain sophistication spans the entire length of the chain, from input sourcing, through production and inventory management, to distribution. At the front end of the chain, we need only be reminded of the heparin disaster of a few years ago to appreciate the weaknesses in quality assurance and supplier management for key inputs. At the distribution end of the supply, the bio/pharmaceutical industry has been under attack regarding counterfeiting and security of supply. A recent article in *Fortune* magazine recounted last year's theft of $75 million of finished drug product from an Eli Lilly warehouse in Enfield, Connecticut (1). The article highlighted the lax security at the warehouse, including failure to monitor security cameras that could have caught the theft while it was taking place (1).

Supply-chain management weakness also can be seen in the way the industry



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manages its inventories. On average, the global bio/pharmaceutical companies turn their inventories a little more than twice a year. They typically have inventory on hand equivalent to about 180 days' worth of sale. By contrast, a best-practice consumer products firm, such as Procter and Gamble, turns its inventory about six times a year and has about 60 days' worth of inventory on hand. As global bio/pharmaceutical companies are trying to maximize their cash-on-hand to help them weather the patent cliff and take advantage of licensing and acquisition opportunities, keeping so much cash tied up in inventory is a real competitive disadvantage.

Opportunity for contract services

The supply-chain management challenges facing the bio/pharmaceutical industry represent a major opportunity for providers of contract services, especially those in manufacturing (i.e., contract manufacturing organizations [CMOs]) and packaging. Because of their critical position relative to both the upstream and downstream segments of the supply-chain, CMOs and packagers are well positioned to help bio/pharmaceutical companies manage their risk and squeeze cost and inventory out of the system.

We have seen isolated instances of contract services providers responding to supply-chain management opportunity (e.g., Patheon's recent efforts to promote its services as a backup source of supply and Almac's short-run packaging services). We've also seen some major providers of third-party logistics services (3PL), such as UPS, DHL and FedEx, make greater efforts to address the bio/pharmaceutical industry.

However, the big opportunity will come when service providers, especially CMOs, figure out how to increase the flexibility and responsiveness of their own operations. For instance, every day that a CMO can knock off the manufacturing schedule lock-in requirement from its traditional three months can save its bio/pharmaceutical company clients millions of dollars in cash tied up in inventory. Further, the internal process changes necessary to achieve those scheduling improvements are likely to deliver substantial cost savings and increased throughput. Given that most CMOs operate well below full capacity, such flexibility should be attainable.

CMOs have traditionally focused on additions to processing technologies, equipment and gain-to-gain incremental volume. Given the supply-chain challenges facing the bio/pharmaceutical industry, a focus on operations excellence in the context of supply-chain management is likely to yield greater performance for both the client and CMO and yield market share gains going forward.

Reference

1. K. Eban, *Fortune*, Mar. 31, 2011, http://features.blogs.fortune.cnn.com/2011/03/31/drug-theft-goes-big/, accessed Apr. 11, 2010. **PT**

Inside USP

contin. from page 90

direct impact on setting the resulting USP standard, which provides an appropriate standard to be enforced by regulatory authorities. To acknowledge the generosity of donors, USP recently enhanced and expanded its Donor Recognition Program. Elements include a Certificate of Appreciation; public recognition (for those donors who wish to be recognized) in formats such as the *USP–NF* or during scientific meetings; donor-specific progress reports; and complementary or discounted USP products and services.

To maintain consistency with FDA–approved specifications and control strategies, USP prefers to receive submissions from manufacturers of FDA–approved products (including drug substances and excipients used in FDA–approved products) or manufacturers seeking FDA approval. The latter category of submissions will be considered for publication as Pending standards. Submissions, especially new impurity procedures, from other sources (e.g., contract laboratories, academic institutions, analytical instrumentation or equipment manufacturers) will be accepted on a case–by–case basis and should follow the International Conference on Harmonization's Q3 guideline. Some modernization proposals may generate new USP Reference Standards, and USP invites the sponsor of the proposal to donate the necessary bulk reference materials.

Manufacturers may be concerned that updated monographs will lead to added costs for corresponding upgraded equipment and processes. However, many manufacturers of the medications involved have already, of their own initiative, improved tests since the monograph was first published. These updates occur regularly as technologies and methods advance. In fact, USP is hoping to take advantage of these types of initiatives and growth areas so that they may be reflected in the compendia through updated tests and limits.

The partnership among USP, FDA, and CHPA represents a united front in the effort to safeguard public health. USP appreciates and strongly encourages widespread industry participation early in the monograph-modernization process.

For more information

- Details about the monograph modernization initiative, including FDA's priority list, can be found online at www.usp.org/hottopics/monographs.html.
- Details about the Donor Recognition Program are available online at www.usp.org/referenceStandards/participate.html.
- Details about submitting revision requests can be found in the *USP Guideline for Submission of Request for Revision* and in the USP Submission Checklist, available at www.usp.org/USPNF/participate.html and www.usp.org/USPNF/submitMonograph/subGuide.html, respectively.
- Details about submitting reference standards can be found in the *USP Guideline for Suppliers of Reference Standard Materials at* www.usp.org/referenceStandards/participate.html.
- To review and comment on the proposed revisions, including proposals for revisions not listed, see the latest edition of the *Pharmacopeial Forum*. **PT**

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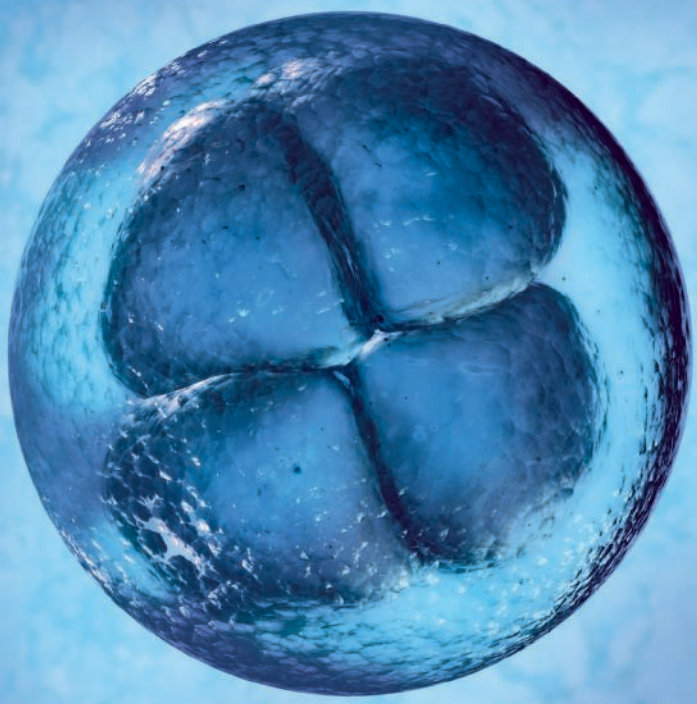

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From left to right: Suzanne Fillweber, eastern sales manager, and Mike Tracey, publisher, both of *Pharmaceutical Technology* and Advanstar Communications, present an award to Andy Honeycheck, marketing communications manager, and Firouz Asgarzadeh, principal scientist, both of Evonik Pharma Polymers.

Evonik Wins Award for Extrusion Webinar

Advanstar Communications, which publishes *Pharmaceutical Technology,* presented Evonik Pharma Polymers with the award for the "Highest Number of Webcast Pre-Registrants in 2010" for the company's webinar titled "Pharmaceutical Melt Extrusion: A Strategy for Poorly Soluble Drugs." The webinar, held on Sept. 14, 2010, attracted 1148 preregistrants and had a view rate of 607 (i.e., 53%), thus making it the company's most viewed webcast of 2010.

The webinar offered insight on solid-dispersion technologies used to enhance solubility when formulating poorly soluble drugs. Panelists included Navnit H. Shah, distinguished research leader at Hoffmann-La Roche, and Firouz Asgarzadeh, principal scientist at Evonik Degussa Pharma Polymers.

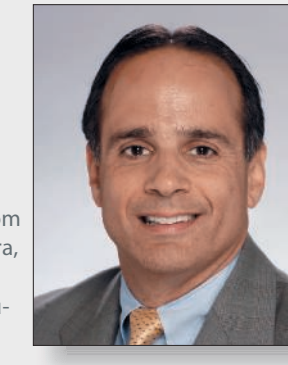
AAIPharma Expands Its Compendial Testing Facility

AAIPharma Services relocated its compendial raw-materials testing group to a new, purpose-built laboratory space located within the company's Wilmington, North Carolina, headquarters facility. The move follows a series of recent reinvestments into the company's core analytical testing business.

The new laboratory will integrate the compendial raw-material testing laboratory and its supporting business group under one roof, and will increase turnaround times for raw-materials testing. The new laboratory space includes state-of-the-art engineering controls, an updated information-technology infrastructure, and updated gas-generation systems to support the dedicated gas chromatographs for improved sample throughput.

Q&A with

Greg Irace, *president of sanofi-aventis*



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

Irace:
I'd say the biggest challenge we're all facing is change. From the end of the blockbuster era, to the impact of healthcare reform, to a challenging regulatory environment and the changing dynamics between patients, payors, and providers, the entire context in which we operate is changing.

Globally, sanofi-aventis has taken many steps to stay ahead of the curve and address these challenges. First, we are diversifying our business. We now consider ourselves not just a pharmaceutical company, but a diversified healthcare company. In addition to our pharmaceutical and vaccine businesses, we have built a significant presence in consumer health, animal health, and emerging markets. We are also being more strategic about how we allocate resources; we're now concentrating on high-growth areas, including diabetes, oncology, and atrial fibrillation. Ultimately, we work with our partners to protect health and enhance life. I believe these moves will set us up for long-term sustainable growth.

PharmTech:
Do you see a new industry trend emerging?

Irace:
We are excited about the trend of using a decentralized approach. Companies are forming disease-based units with their own experts dedicated to research and development, regulatory affairs, marketing, and sales. The goal of this approach is to bring the best and brightest minds and methods to bear early on in the development process of a potential treatment and to leverage those resources throughout the product's life cycle.

Recognizing patients' evolving needs and the challenging environment in which we are operating, sanofi-aventis US has adopted a decentralized model. We hope this approach will result in greater efficiencies—improving the likelihood of success by focusing efforts on fewer projects with greater potential—and improved innovation, ultimately benefiting patients.

We're also energized by developments in the medical-device arena that have the potential to change the way patients manage their conditions. sanofi-aventis US offers various devices to simplify insulin use for patients.

MANUFACTURING EQUIPMENT & SUPPLIES

Multishaft mixer

The Sanitary VersaMix multishaft mixer breaks down agglomerates, accelerates homogenization, and prepares fine droplets in an emulsion. The VersaMix processes viscous formulations, including suspensions, pastes, slurries, and gels, and draws powders into the liquid batch through a powerful vortex. Additionally, the low-speed anchor promotes bulk flow and uniform batch temperature while scraping the vessel bottom and sidewalls. **Charles Ross & Son,** *Hauppauge, NY • www.mixers.com • tel. 800.243.ROSS*

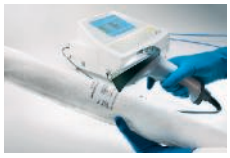
Capsule filler

The Adapta machine is designed to adapt to customers' requirements. Two of the device's dosing units are reversible and interchangeable, thus allowing a plug-and-play shift between various configurations and filling combinations. The machine can dose three products into the same capsule at a speed of 100,000 capsules/h. Total production control is available. **IMA North America,** *Leominster, MA • www.ima.it • tel. 978.537.8534*

Sterile disconnectors

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

MANUFACTURING EQUIPMENT & SUPPLIES



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*

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*

Protein purification

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

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*

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*

Nano-16 twin-screw extruder

A nano-16 twin-screw extruder with 16-mm outer diameter screws and a 1-mm flight depth was designed to evaluate extrusion with as little as a 20-g batch. Screws and barrels are segmented, and the extruder uses trilobal screw elements. A 1.2:1 outer diameter:inner diameter ratio results in a free volume of approximately 1 cm^3/diameter. **Leistritz,** Somerville, NJ • www.leistritz-extrusion.com • tel. 908.685.2333

MANUFACTURING EQUIPMENT & SUPPLIES

Tablet-coating platform

The Accela-Cota FLEX 500 tablet-coating platform features six exchangeable drums and provides an overall batch-size range of 50–820 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*

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*

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*

MANUFACTURING EQUIPMENT & SUPPLIES

End-ported biocontainers

Meissner's end-ported TepoFlex biocontainers are made of the company's polyethylene-based film. The biocontainers have been optimized for single-use system requirements within the biopharmaceutical industry and are available in sizes from 50 mL to 20 L. The units offer strong barriers to gas and water vapor to protect products. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Pump tubing

Saint-Gobain has introduced its C-Flex ULTRA pump tubing. Designed to outperform current thermoplastic elastomers, the C-Flex ULTRA tubing is heat sealable, weldable, and doesn't clog pump heads. The product's clear plastic complies with US Pharmacopeial standards. **Saint-Gobain Performance Plastics,** *Clearwater, FL • www.biopharm.saint-gobain.com • tel. 800.541.6880*

Container closures

BioClosure Systems are a line of container closures suited for clean pharmaceutical, biotechnology, and laboratory applications. The closures are practical for repeated or single use and work with flexible container systems, laboratory bottles and apparatuses, and sampling and storage receptacles of glass, plastics, or metal. **AdvantaPure,** *Southampton, PA • www.advantapure.com • tel. 888.755.4370*

OUTSOURCING & CONSULTING SERVICES

Outsourced research services

MPI Research is a contract research organization for preclinical and clinical services, including discovery, safety, bioanalytical, and analytical sciences. MPI Research encourages its experienced staff to be responsive to client needs, and the company takes a collaborative approach to its customers' projects. MPI places importance on maintaining enduring relationships with its sponsors. **MPI Research,** Mattawan, MI • www.mpiresearch.com • tel. 269.668.3336

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*

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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*

OUTSOURCING & CONSULTING SERVICES

Lyophilization services

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*

Development service

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

Contract manufacturing

SAFC is ready to meet clients' contract-manufacturing needs with high-quality products, helpful ideas, and excellent service. The company works with its customers every stop of the way and attempts to anticipate their needs and offer keen insight. **SAFC,** *St. Louis, MO • www.safcglobal.com • tel. 314.771.5765*

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-ft^2 facility to ensure that clients' clinical and commercial products meet high standards. **WellSpring Pharmaceutical Canada,** *Oakville, Canada • www.wpcoutsourcing.com • tel. 866.337.4500*

Fill–finish services

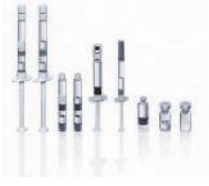
Cangene bioPharma, formerly Chesapeake Biological Laboratories, is a leading provider of high-quality fill–finish services in vials and syringes. Cangene bioPharma has a strong regulatory profile, including excellent regulatory compliance with US, EU, and Japanese regulations. Cangene has helped produce more than 20 commercial and 185 clinical products for customers for distribution worldwide. **Cangene bioPharma,** *Baltimore, MD • www.cblinc.com • tel. 800.441.4225*

Lyophilization

DSM offers a lyophilization system with the precision to serve demanding cycles. DSM's lyophilizers are equipped with LyoAdvantage software for cycle control, which provides the accuracy necessary for high-value products. The system enables scale-up from an 8-ft^2 unit that does not comply with good manufacturing practice to any commercial unit. **DSM Pharmaceuticals,** *Greenville, NC • www.dsmpharmaceuticals.com • tel. 252.707.4376*

OUTSOURCING & CONSULTING SERVICES

Drug-delivery systems



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

Controlled packaging environment

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

Containment capabilities

Lyophilization Technology has on-site containment capabilities for highly potent compounds, oncology therapeutics, and biologicals. The company's qualified facility features negative-pressure isolators for primary containment within an ISO 7 room and ISO 5 processing areas. The company seeks to safeguard products' integrity and provide high quality. **Lyophilization Technology,** *Ivyland, PA • www.lyotechnology.com • tel. 215.396.8373*

OUTSOURCING & CONSULTING SERVICES

Analytical pharmaceutical services

AAIPharma takes a customer-focused approach to solving drug-development and manufacturing challenges. The company's analytical pharmaceutical services include clinical packaging and distribution, sterile and solid-dose manufacturing, analytical services, validation, regulatory-affairs consulting, formulation development, and oral drug-delivery technologies. **AAIPharma,** *Wilmington, NC • www.aaipharma.com • tel. 910.254.7000*

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 pass-through chambers

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

PACKAGING EQUIPMENT & SUPPLIES

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*

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*

LABORATORY EQUIPMENT & SUPPLIES

Glove boxes

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

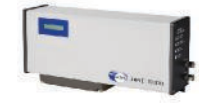
LABORATORY EQUIPMENT & SUPPLIES

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*

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*



Total-organic-carbon analyzer

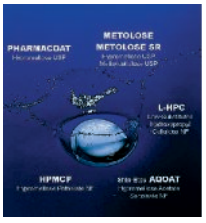
The Anatel TOC600 on-line total-organic-carbon analyzer is designed for pharmaceutical water measurement. Its patented stop-flow oxidation technology provides complete oxidation of an aliquot of water and fully complies with *USP* <643> and *EP* 2.2.44. The Anatel TOC600 unit's wide dynamic range allows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

LABORATORY EQUIPMENT & SUPPLIES

On-line TOC analysis

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

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS



Excipients

Shin-Etsu Chemical's low-viscosity Pharmacoat grades are film formers and granulation binding aids. The company's Metolose and Metolose SR excipients are designed for thickening liquids and formulating sustained-release matrices. Shin-Etsu also offers hydroxy propyl methyl cellulose phthalate and its Aqoat product for enteric coatings. **Shin-Etsu Chemical**, *Tokyo • www.shinetsu.co.jp • +81 3 3246 5261*

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Chemicals

More than 15,000 of Spectrum Chemical's products are available through Lab Safety Supply, a leading provider of laboratory, safety, and other industrial products to more than 800,000 customers in North America. **Spectrum Chemical Manufacturing,** *Gardena, CA • www.spectrumchemical.com • tel. 800.901.5516*

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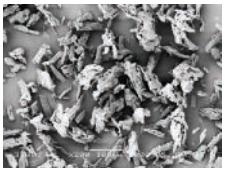

Microcrystalline cellulose

Ceolus UF-711 is a highly compactible micro-crystalline cellulose with excellent powder flow. It comprises comparatively round and porous particles that contribute to high flow and compactibility. The product enables the creation of small tablets and challenging formulations. The ingredient is designed for direct compression using a gravity feeder. **AsahiKASEI America,** *New York, NY* • www.ceolus.com • tel. 212.371.9900

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*

Polyethylene glycol

Carbowax Sentry low-aldehyde polyethylene glycol excipient grades 300, 400, and 600 are well-suited for gelatin capsules or liquid formulations in which aldehyde impurities decrease stability. Clear, viscous grades resist rancidity and microbial growth and carry a low specification limit for ethylene glycol, which helps high-dose products comply with USP <467> standards. **The Dow Chemical Company,** *Midland, MI • www.dow.com • tel. 800.447.4369*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

MACRON™ CHEMICALS
Formerly Mallinckrodt® Chemicals

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*

Website

Roquette has launched a website for its pharmaceutical division. The site grants access to the company's excipient and active product lines and offers information about services. A formulation tool provides assistance to formulators from the product development cycle through to launch. The special services and support sections describe Roquette's application expertise. **Roquette,** *Keokuk, IA • www.roquette-pharma.com • tel. 319-524-5757*

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

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uncover manufacturing problems and that unfortunately, FDA does not have the resources it needs to perform all of its targeted biennial inspections. As a result, consumer complaints and other triggers often prompt the agency to inspect OTC manufacturing sites.

On the positive side, FDA recently released a guidance for industry on adverse-event reporting that requires manufacturers of OTC monograph drugs to provide safety updates to the agency (9). But until FDA's budget sees a massive increase, inspections of facilities, and seemingly low-risk facilities, may be put on the back burner.

Checking expectations

Many of the ongoing efforts described herein are aimed at improving OTC drug safety for consumers, and says CHPA's Spangler, "It doesn't take a whole lot of sophistication to observe that we're in an era of greater enforcement." These changes are good, he says, because industry ultimately wants to reassure consumers that products on the market are safe and meet quality standards.

That said, it is not official that OTC drug manufacturers will face higher levels of enforcement going forward. According to FDA, the agency's "standards that a marketed drug must have a favorable benefit-to-risk profile remain unchanged."

At the end of the day, consumers play a crucial role in OTC drug safety by their decisions to select and use these products properly. "Consumers should read the product labels carefully and should not throw away the boxes that have the Drug Facts information," points out FDA's Kubaska. Together, consumers, industry, and the authorities can make the drugstore shelf not just an easily accessible place, but a safer place.

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India's Biotech Industry is Poised for Exponential Growth

Alan Eisenberg

India has the potential to become the new star of the biotechnology industry.

India is home to a robust and growing biotechnology industry because of the country's increasing premium on innovation. Maintaining and sustaining this sector, however, requires active support from government, policymakers, academia, the financial community, and others.

Biotechnology promises solutions to many of the global challenges faced by the world, and industry leaders in India recognize the myriad benefits of further developing a robust biotechnology sector within the country. Policies to encourage biotechnology investment and development will produce a significant return on investment by creating high-skill, high-wage jobs and bringing innovations to market.

Last Fall, the Biotechnology Industry Organization (BIO)and the Association of Biotechnology Led Enterprises (ABLE) hosted the inaugural BIO India International Partnering Conference in Hyderabad, to bring together biotechnology and pharmaceutical companies from North America, Europe, and Asia to explore business opportunities within India's emerging biotechnology sector. Leading companies and industry experts from India and around the world attended the conference as did many investment industries.

Global biotech companies will continue investing in India as long as India continues investing in biotechnology.

There is significant global competition engaging the biotech sector globally and it was clear at the conference that many multinational biotechnology and pharmaceutical firms have set their sights on India. They are eagerly entering into resaerch and development partnerships as well as licensing and distribution agreements with Indian companies.

But questions remain. Will India, for example, establish the regulatory system, public policies, and incentives it needs to encourage and support innovation?

Discussions at the 2010 BIO India meeting highlighted the need for a concerted effort to develop a comprehensive regulatory framework for the approval of biologics in India, including the approval of biosimilars. For example, the Indian government must set approval criteria for biologics and biosimilars that protect patient safety *and* preserve incentives to innovate. Well-crafted pathways for the approval of these drugs will lower costs by increasing competition and promote further biomedical research and development. BIO has created a list of principles on biosimilars which is available online (http://bio.org/healthcare/).

BIO recognizes the efforts of the Indian government to streamline the various authorities impacting the nation's biotechnology sector and we applaud the open channel of communication between the Department of Biotechnology and the Drugs Controller General of India. These efforts, in conjunction with the Indian government's willingness to hear from various stakeholders, will be useful in shaping India's regulatory framework which, in turn, will generate investment interest in biotechnology. The Indian government also is working on economic programs to bolster its established biotech clusters, and the National Institute of Public Finance is drafting a plan to establish a venture capital-type fund to finance drug-discovery projects across the country.

India's biotechnology industry holds the potential for boundless growth. Global biotech companies will continue investing in India as long as India continues investing in biotechnology. BIO stands ready and committed to working with biotechnology leaders in India to deliver on the enormous promise and potential of their biotech sector. **PT**

Of note, BIO India will be held Sept. 21–22 in Hyderabad.

Alan Eisenberg is the executive vice-president of Emerging Companies and Business Development for the Biotechnology Industry Organization (BIO).

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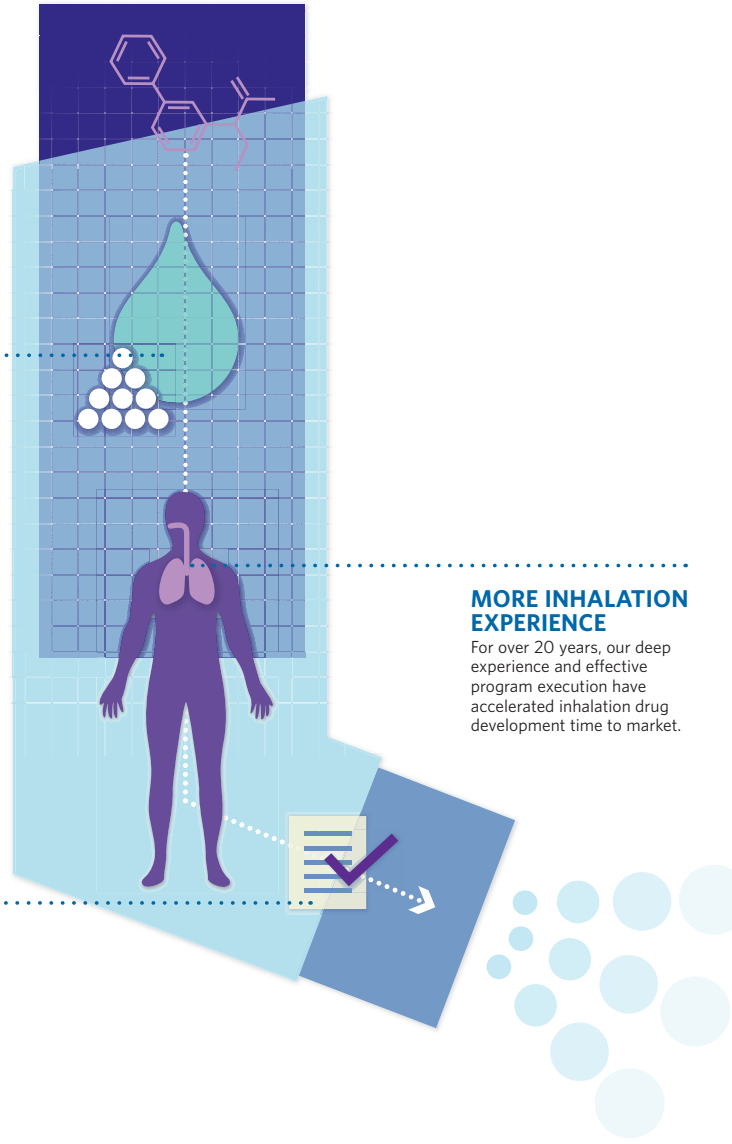

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