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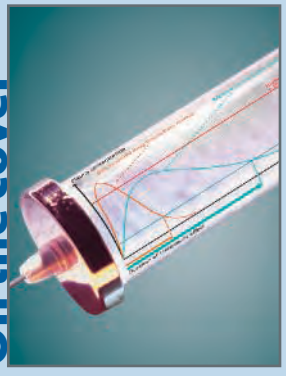

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Legislation v. Litigation

Michelle Hoffman

Which route will we take to arrive at a national stem-cell policy?

In the course of every relationship, there arise moments for the "difficult conversation." Usually it's of the "where are we headed with this?" variety. But that's really just part of a larger question: Do we have a shared philosophy, and what is it?

Whether we think of it that way, nations ask themselves this question routinely. Should our nation be guided by a religious philosophy, or not? Should we elect our leader as a group, or should a person ascend to leadership through inheritance? If the times require us to alter our viewpoint, do we decide as a group, or does someone decide for us, and if so, who?

Sometimes the answer is explosive: Whoever we are, it's not working, and we need to change now.

That's the kind of answer that can lead to revolutions. In the US, we've mostly dealt with the question of our national ethic more quietly, starting with the first national conversation, which lay out a basic philosophy in the form of a constitution. Nevertheless, there have been many difficult conversations we've failed to have as a nation. To whom do we accord full citizenship, for example? Not even the Founding Fathers could agree on this one, thereby establishing the alternative to a national conversation: the local conversation. Instead of making a national decision about which people could own land, vote, or intermarry, those questions were left to local governments.

Potential use of embryonic stem cells pits technology against notions of personhood.

In these cases, challenging and sometimes overturning local philosophies (and sometimes overturning them again) has been, not through legislation, but through the courts, through litigation. That's how we've handled teaching evolution in schools, gay marriage, and abortion—locally and through litigation.

Some conversations, it seems, are just too difficult to have nationwide. I expected the conversation about stem-cell therapies to be one of those too-difficult conversations as well, one that would also be handled case by case and concession by concession—through litigation rather than legislation.

So it came as a surprise to learn that in mid-May, US Representatives Brian Bilbray (R-CA) and Diana DeGett (D-CO) introduced the Regenerative Medicine Act of 2011 (H.R. 1862). The Act notes that, "Regenerative medicine products have already successfully treated numerous health conditions, and have the potential to provide cures, treatments, and diagnostics for a range of diseases and disabilities including diabetes, spinal cord injury, heart disease, stroke, and various forms of cancer."

The proposed legislation goes on to say, "A United States national strategy on regenerative medicine is critical to ensure that this technology fulfills its potential to cure and treat diseases and disabilities, reduce overall health spending, and promote economic growth."

Not once does the Act mention stem cells, embryonic or otherwise, which are among the therapeutic agents used in regenerative medicine. It is the potential use of embryonic stem cells that makes a national conversation difficult, because, like the still-unresolved abortion debate, it pits technology against notions of personhood. Indeed, the stem-cell debate has already been the object of some well-publicized litigation. And it seemed likely that the entire debate would continue that way.

Whatever the fate of the Regenerative Medicine Act of 2011, I hope it sets a precedent for the way we discuss novel, but potentially ethically thorny issues of technology in the future. After living together as a nation for 235 years, shouldn't we at least know how to broach difficult conversations? **PT**

Read more on the topic of regenerative medicine on page 134.

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

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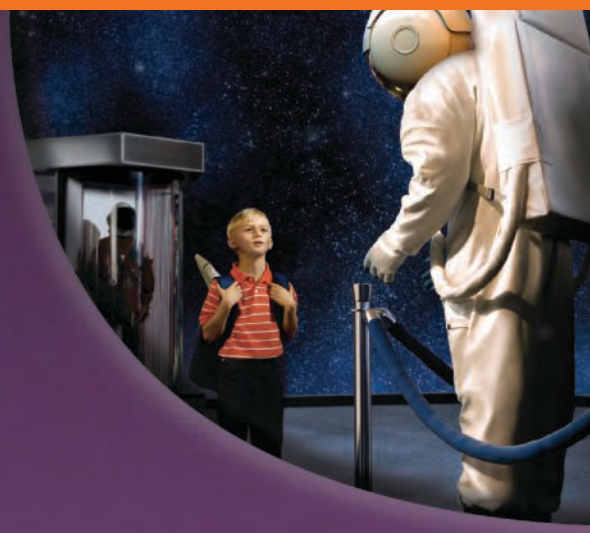

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Pharma Leads in Sustainability

Angie Drakulich

Sustainability is about more than going green. When it comes to business strategy, it also includes social and corporate governance, according to a definition from consulting firm Brandlogic and investment analytics firm CRD Analytics. The companies recently released a survey about the real and perceived sustainability efforts of the top 100 companies around the world. The goal of the *Sustainability Leadership Report: Measuring Perception vs. Reality* is for industry to use the identified gaps between real and perceived sustainability efforts to improve corporate performance.

The good news is that the pharmaceutical/healthcare industry, one of nine sectors included in the survey, is leading the way in corporate sustainability. Other sectors included consumer, energy, financials, industrials and transportation, information technology, materials and mining, and telecommunications and Internet. The study authors used data from survey participants to establish a sustainability IQ matrix which groups companies into one of four areas: laggards (low perception, low reality), promoters (high perception, low reality), challengers (low perception, high reality), and leaders (high perception, high reality). Groups are based on real and perceived scores, both of which incorporate key performance indicators such as the company's environmental emissions, social diversity, and corporate vision.

Abbott Laboratories, AstraZeneca, Bayer, GlaxoSmithKline, Johnson & Johnson, Merck, Novo Nordisk, and Pfizer all ranked in the "leader" category. Roche fell into the "challenger" category; BASF fell into the "promoter" category; and no one from pharma ended up in the "laggard" field.

The industry's activities in environmental, social, and corporate governance come as no surprise. The most nascent goal of the drug-manufacturing world is to improve health, and ultimately, to improve lives. More and more, industry is realizing that social, environmental, and governance sustainability initiatives—and not just its products—can help it achieve this goal. **PT**

Angie Drakulich is the senior managing editor of *Pharmaceutical Technology*.

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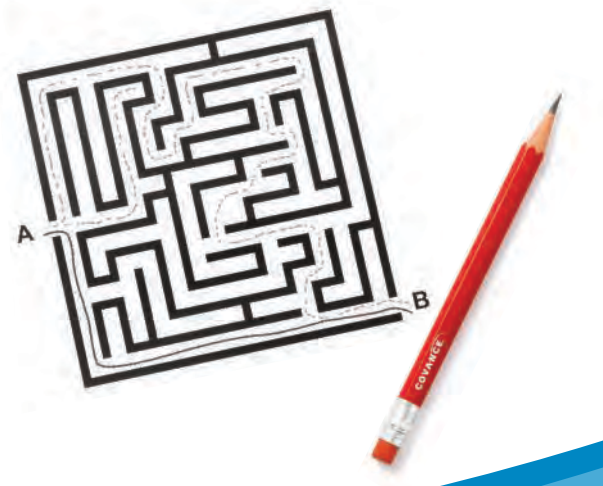

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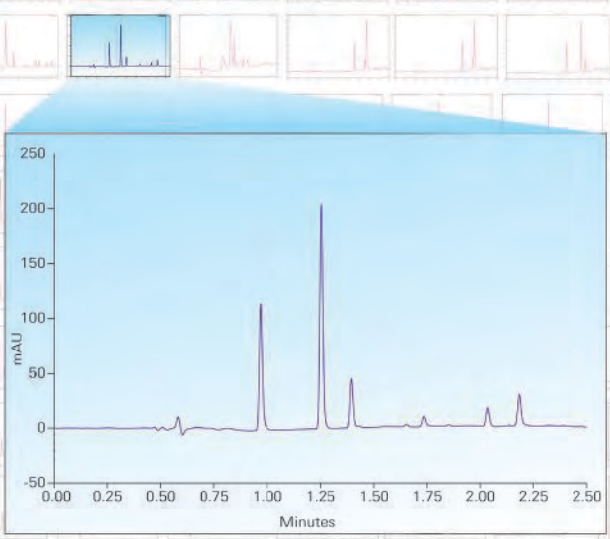

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All the Wrong Questions

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

Getting an answer is easy—asking the right question is apparently more difficult.

Banana splits, anyone?

"We validated it," our GMP Agent-In-Place swore. "We received test syringes and ran them through the labeling machine. They worked perfectly. But the manufacturing setup mechanics must have set up the labeling equipment incorrectly. There was so much breakage. It is an expensive product, and the breakage meant lost income and delays. The investigation started with a call to our European colleagues who use the same syringe. In fact, the validation quantities had come from their stocks. We were unaware that new syringes had been manufactured by a North American factory, rather than by the European syringe factory," moaned our Agent. "The North American syringes were actually banana-shaped, with a bit of a curve. When they were rolled along the labeling machine, pressure caused the breakage. Our validation had used the 'best-case scenario' syringes."

Objective inspection

"At the end of the year, we filled out our self-evaluation forms based on year-long objectives," our GMP Agent-In-Place sighed. "Among other things, I was responsible for hosting inspections, but that duty never shows up on the objectives list because it is essentially a job-description requirement. I was upset because I could only demonstrate that 20% of my objectives had been reached. When I added up the inspection days I spent with FDA, the US Drug Enforcement Agency, the US Bureau of Alcohol Tobacco and Firearms (we used 1 million gallons of denatured alcohol per year, and they want accounting for it), the US Department of Agriculture, and health authorities from Germany and the United Kingdom, however, I realized that I had been involved in 202 inspection days."

On the bubble

"One thing I like to check when auditing is whether the balances or scales are level," began our GMP Agent-In-Place. "Most of them have a bubble indicator, and the bubble should appear inside the circle for proper operation. You'd be surprised how often I find the scales off level. After moving a scale, good practice involves performing at least a two-point check with certified weights on the scales and balances. A best practice is a full recalibration."

Helping out

"Sometimes we get involved in activities outside our department, even if it is just answering a question," our GMP Agent-In-Place explained. "We had a new employee who was responsible for the safety program. A woman from the research and development division hurt her back while lifting a product container. We use metric measurement for everything, and the safety manager was used to American-standard measures. He didn't realize how much 60 L of product would weigh when we told the woman she could move it—it actually weighed about 140 pounds (given the density of the material). The container was a large bulky item for anyone to be lifting and repositioning."

Budgeted compliance

"Site projects were often prioritized by the site manager," noted our GMP Agent-In-Place. "The goal was to move projects forward based upon compliance and quality at each site, so after a year of politicking, we had a $200,000 budget for use in unplanned quality projects at the discretion of the worldwide vice-president for quality. One site head read the budget in full, and as soon as the new budget year began, he requested funding from our stash. He wanted to paint hallways and the guardhouse, claiming that the result would be improved morale which would ultimately improve quality. The request was rejected."

Substandard substrate

"Ouch," winced our GMP Agent-In-Place. "Our contract manufacturer owns the product license and decided that we had to recall several batches of product. The product was sold based on the potency in the vial; more potency means higher prices. The potency is labeled on the vial and differs from batch to batch. On the recalled batches, the potency was too high. When we asked why the labeled potency was so high, the manufacturer explained that they had changed the assay substrate, and it was resulting in a higher potency than desired. Simply put, we had failed to properly validate the method change." **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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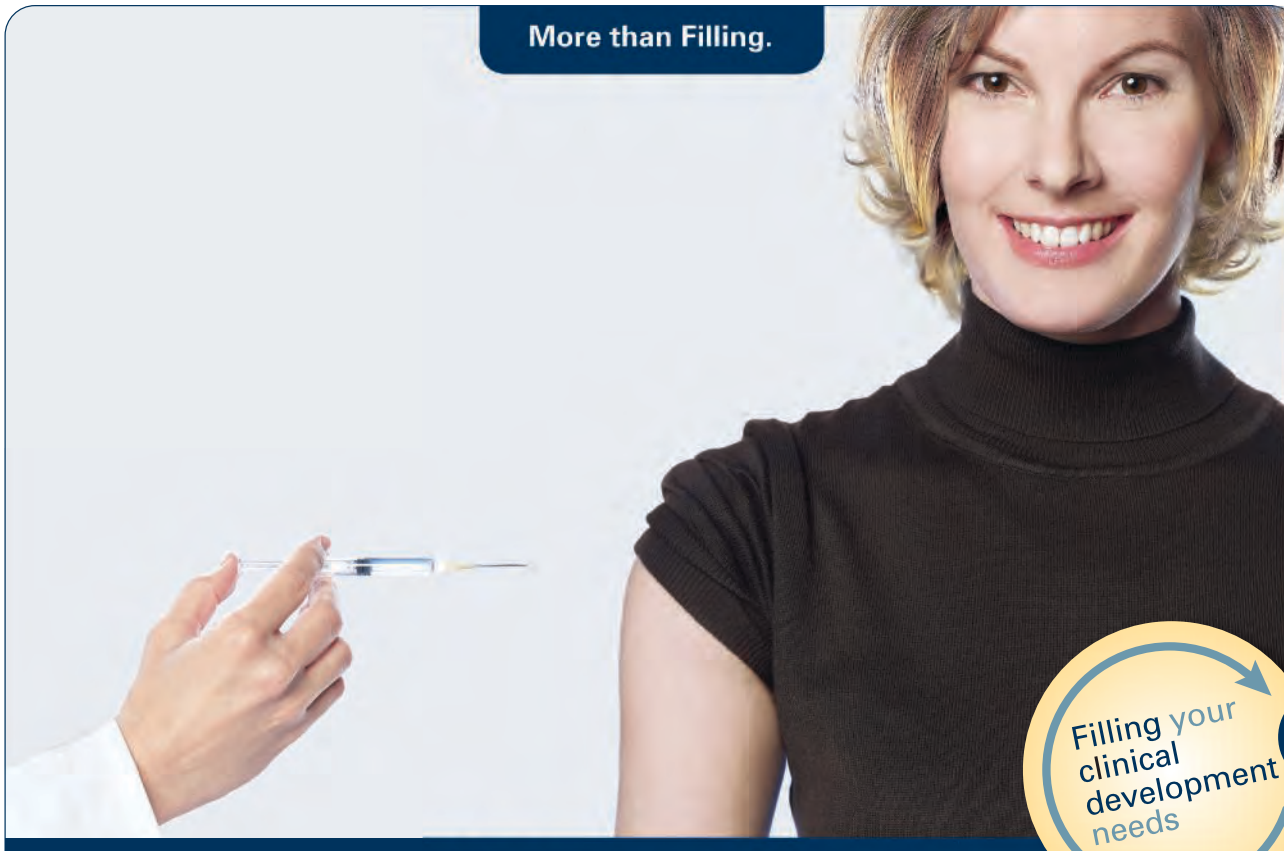

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Report from: Europe

Sean Milmo

Member states in the European Union are working to implement the newly passed Falsified Medicines Directive.

Three years after first being drafted, new regulations on combating the growing menace of fake medicines have finally been approved by the European Union. It has involved intense lobbying by trade associations in the sectors most affected by the legislation—the drug manufacturers themselves, producers of active pharmaceutical ingredients (APIs) and excipients, and packaging suppliers. There are still, however, issues to resolve.

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Many of the details of the legislation, the Falsified Medicines Directive (FMD), have yet to be worked out. The EU legislative body, which consists of the European Parliament and the Council of Ministers, represents the governments of the union's 27 member states. The legislature has decided to delegate the task of finishing the job to the European Commission, the EU's executive body. After that task is complete, any additional details will still have to be approved by the two legislative arms before finalization and implementation can occur.

"We're pleased with what we have got but we've got reservations about the details because there are a lot of unanswered questions about how the legislation will be implemented," says Tony Scott, adviser to the European Fine Chemicals Group (EFCG), which represents European-based API producers.

During the next 18 months and before the FMD's implementation, EU states will have to incorporate the directive into their national statutes. Some experts believe that the Commission could take much longer than this allotted timeframe to fill in the gaps, particularly with regard to the new rules regarding APIs and packaging.

Most APIs used in Europe are imported, mainly from India and China. The European fine-chemical manufacturers failed to persuade the legislators to agree to a mandatory system of official inspections to ensure that API plants comply with GMPs. European API producers have long complained about unfair competition from substandard Asian imports.

Instead, the legislation makes auditing of API plants by drug manufacturers obligatory. It also requires countries exporting APIs into Europe to have plant-inspection systems and GMP standards equivalent to those in the EU.

The Commission will have to decide what is "equivalent" and establish a process for verification of equivalence. The legislation appears to be flexible on this matter. It does not lay down, for example, that GMP standards for active ingredients will be the same as those in existing EU regulations.

"The Commission will certainly need to consider a transition period for implementation of this provision (on equivalence in standards of API exporting countries)," says Julie Marechal-Jamil, senior manager for quality and regulatory affairs at the European Generic Medicines Association (EGA).

FMD also makes GMP for excipients obligatory. But it has left to the Commission the decision about what GMP standards must be applied. Excipient producers seem confident that the existing GMPs for food production will be permitted.

With regard to packaging, the legislation stipulates that packaging should enable verification of authenticity, identification of individual packs, and capacity to show tampering evidence. These features would be backed by a pan-European information-technology network that is linked to a central database.

The exact nature of the safety features and the verification system, including any data-matrix characteristics and the size of the centralized databank, still needs to be finalized. The details are likely to be a controversial because they could trigger costly changes in packaging processes and equipment.

Already, the generic-drug sector is demanding exemptions from the scheme on the grounds that generic drugs are the least likely to be counterfeited and that producers of high-priced drugs should bear most of the costs of the changes.

"Manufacturers that have medicines considered at high risk of being falsified should pay (for the costs of the system) by the value of the medicine and not by the volume in the market," says Hugo Carradinha, EGA's senior manager for health economics affairs.

Tighter supply-chain controls for finished medicines as well as for raw materials will offer new openings to chemical distributors, particularly those adhering to good distribution practice, which is also a requirement of the new legislation.

"This legislation is a positive development for us," says Michael Cooke, who is responsible for the pharmaceutical sector at Univar, a leading chemicals distributor in Europe. "Traceability will become of even greater importance with pharma customers needing to be assured that suitable GMP standards are applied to all materials. We've invested in creating robust traceability systems."

Drug manufacturers will be seeking help from suppliers and distributors to reduce the extra costs of the legislation. "Funding of the FMD is a key concern," says Marechal-Jamil. Already, the enforcement of the new regulations faces delays because of a limited budget. Scarcity of funds could be major factor holding up the implementation of FMD as well.

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

- An update on the upcoming United Nations meeting on noncommunicable diseases and the pharmaceutical industry related role
- A case study of sustainability at work in the pharmaceutical industry
- A roundup of CSR and sustainability news.

We welcome your ideas to learn about the work of your company or organization in CSR and sustainability. Past issues have addressed IFPMA's outline for global health initiatives, technology transfer, access to world markets, and more. Contact Patricia Van Arnum, senior editor, with your ideas at pvanarnum@advanstar.com.

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Global Healthcare on the Ground

GSK Works in Developing Nations to Improve Everything from Research to Roads

Angie Drakulich

GlaxoSmithKline (GSK) has been leading several industry efforts during the past decade to improve healthcare among developing-country populations. In 2001, the company dedicated a research and development (R&D) facility in Tres Cantos, Spain, to developing new treatments to combat diseases in the developing world. GSK now operates an open laboratory at the facility, which offers researchers from around the world a place to collaborate on new medicines for neglected diseases.

Pricing and partnerships

GSK also offers preferential pricing as well as not-for-profit pricing of its antiretrovirals (ARVs) to developing nations which helps to improve access to the needed drugs. The program reaches 69 of the world's poorest countries. In addition, approximately 75% of the company's manufactured vaccines are sold to developing countries on a tiered-pricing plan.

GSK has established community investment activities and partnerships that foster healthcare practices in places such as sub-Saharan Africa, Asia, and South America, and has launched several partnerships aimed at finding solutions for global healthcare problems.

"Developing countries face multiple issues on a systemic basis that negatively affect health outcomes for their citizens," says Jon Pender, vice-president for intellectual property and access at GSK, about the company's global healthcare efforts. "Fundamentally, poverty both makes people sicker and makes it harder to tackle healthcare challenges. Many people living in poverty do not have enough food or clean water. In this context, a healthcare system may exist only in name or only in isolated pockets within a country. For example, Africa suffers 24% of the global disease burden yet has only 3% of the world's health workers and 1% of the world's health budget with which to tackle it. There is no way you can get those numbers to add up to adequate healthcare provision. Together, the public and private sectors and civil society have helped to galvanize more resources for global health and reduce the barriers to access to medicines. GSK sees itself as a part of this movement and is specifically addressing issues where our talents and resources can be deployed to maximum benefit."

A major challenge with regard to developing and delivering needed medicines to developing countries and neglected populations has to do with the long-standing reality of the economics behind R&D, adds Pender. He points out that developing a new medicine or vaccine typically takes 10 to 12 years and costs around $1 billion, including the costs of failures. Traditionally, the lack of a viable commercial return on this investment for diseases that are not prevalent in industrialized markets meant that little research was conducted on these diseases. Today, however, more attention is being paid to previously neglected diseases, such as tuberculosis (TB) and malaria, and new approaches that share the risks and costs of R&D are being pursued, he says. Through product-development partnerships with organizations, such as the PATH Malaria Vaccine Initiative (MVI) and the TB Alliance, the pharmaceutical industry is developing new tools to combat theses diseases.

The past two years have been particularly important for GSK in this regard. In addition to establishing the open research laboratory in Spain, in 2010, GSK made available to the public more than 13,000 potential malaria targets to help scientists globally focus on finding a malaria treatment. The company is also working with PATH–MVI and the Bill & Melinda Gates Foundation to develop a vaccine against malaria. The vaccine is in Phase III clinical trials at 11 sites across seven countries in Africa.

The company also established an R&D unit focused on developing late-stage products and formulations for diseases that affect populations in the emerging markets. Other pharma companies are involved, including Amgen, which is working with GSK to make its osteoporosis medicine, denosumab, available in developing countries. Gilead is partnering with GSK to make its drug for hepatitis B, tenofivir, available in China. India's Dr. Reddy's and GSK worked together to move two new cardiovascular branded generic drugs for developing-country populations into development. The R&D unit, meanwhile, has four ongoing late-stage projects in respiratory disease, urology, dermatology, and cardiovascular disease. These projects involve working with regions and countries to understand fully the local needs and to tailor clinical trials to those needs.

Access

The registration of new medicines in many of these targeted countries, however, can be costly, complex, and time-consuming, says Pender. "Too often, regulatory authorities do not have sufficient capacity to deal effectively with numerous and complex product registrations. A possible solution would be the creation of a harmonized registration system that several countries with the same disease priorities can adhere to."

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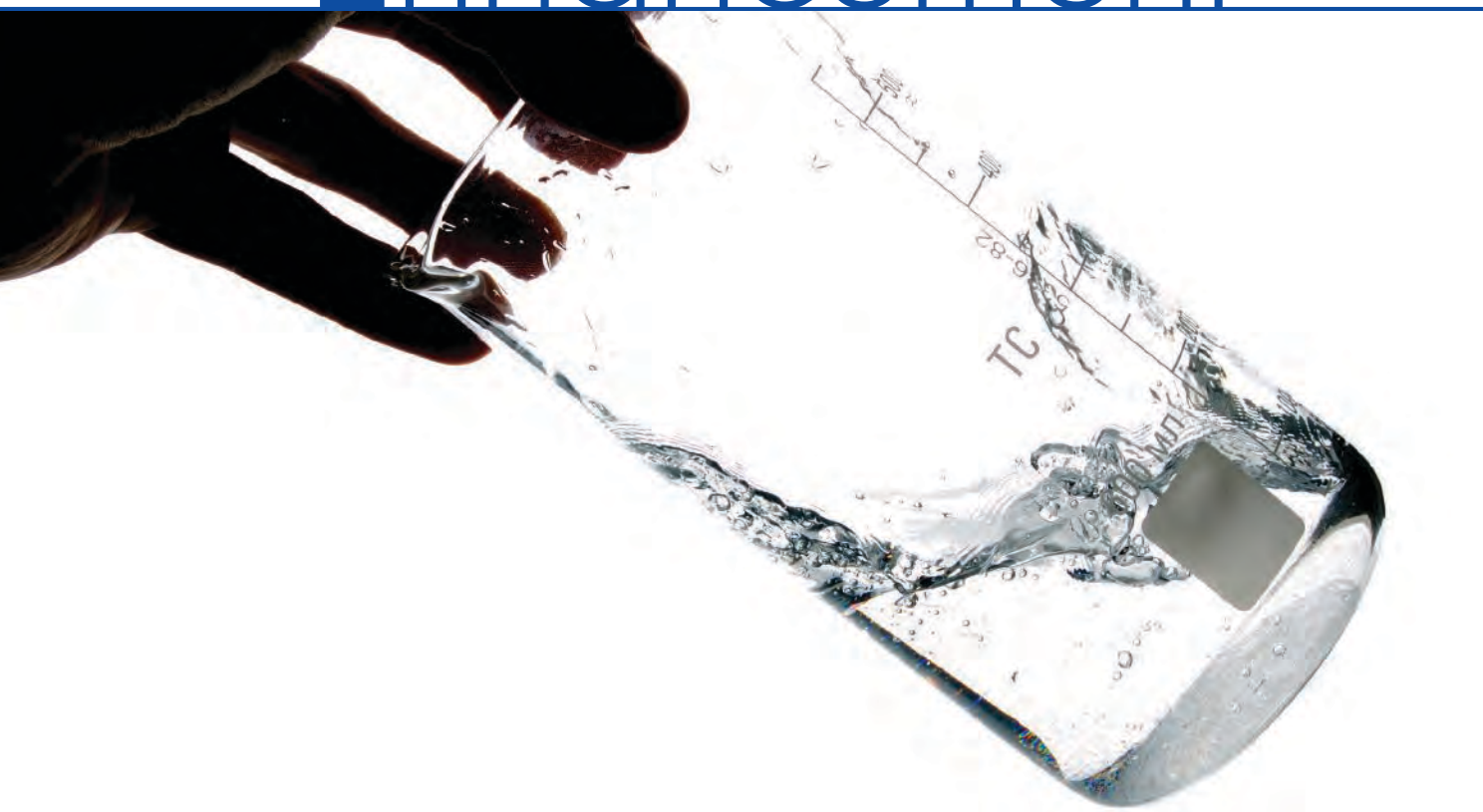
API Delivery Enhancement



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In an attempt to improve this situation, GSK established a dedicated Developing Countries and Market Access operating unit in July 2010. One of the unit's goals is to increase patient access to key medicines and vaccines.

The recently created Advance Market Commitment (AMC), pioneered by the Global Alliance for Vaccines and Immunization (GAVI), offers another financing mechanism to ensure more sustainability in vaccine manufacturing and supply for the developing world. Recently, GSK agreed to supply up to 300 million doses of its pneumococcal vaccine for a period of 10 years to countries that are part of GAVI as part of the first global AMC for the pharmaceutical industry. Pfizer has made a similar commitment for its vaccine.

Infrastructure

Another challenge faced by the healthcare industry globally is the infrastructure that exists in many developing countries, including poor distribution networks and a lack hospitals, clinics, and healthcare professionals. Political issues often compound these barriers, meaning that even when there is funding, there is little action, says Pender. "In middle-income countries, the health system may be more developed, but wide ranges in income mean that many poor people at the lower rungs of the income ladder are not able to access healthcare," he adds. The needs to strengthen health systems and reduce inequities are becoming more visible, and much more can be done to increase access to life-saving services, says Pender.

In the least developed countries (LDCs), the challenge of improving healthcare and access to medicines is even more difficult. Earlier this year, therefore, GSK formed a partnership with AMREF, CARE International UK, and Save the Children to help reinvest 20% of the company's profits made in LDCs back into projects that strengthen the healthcare infrastructure in those countries. The money will go toward programs that improve health outcomes by supporting frontline health workers who operate in these countries.

Since 2009, GSK also has committed to significantly reducing its prices for patented medicines in the LDCs. The company's goal is to reduce prices to no more than 25% of their price in the United Kingdom.

Future plans

Going forward, GSK plans to continue and add to these global healthcare efforts. "All these initiatives commit us to continuing to work closely with the global community and to ensuring the necessary resources and political will are in place to make partnerships work," says Pender. "Partnerships that combine the resources and expertise of companies, governments, international agencies, academic institutions, NGOs and communities, are a central component to our global health approach. From GSK's perspective as a global company, we believe this is not only the right thing to do but makes good business sense. By working with others to find logical and sustainable solutions for the long-term, we can achieve more for patients than we can alone," he adds.

Zone in on: Regulation

FDA Reviews First Year of Bad Ad Program

Erik Greb

After looking back at the first year of its Bad Ad outreach program, FDA judged that the initiative has successfully raised awareness about misleading promotion, according to an FDA press release. The program, which was intended to educate healthcare providers about misleading drug promotions, debuted on May 11, 2010. Since that time, the agency has received 328 reports of potentially untruthful promotion. In contrast, FDA received an average of 104 reports per year before the initiative was launched.

Healthcare professionals submitted 188 of the 328 reports, and 87 of them were identified for comprehensive review. The latter number demonstrates that the medical community has a relatively strong level of knowledge about what constitutes misleading promotion, according to the press release. The agency hopes that doctors' heightened sense of awareness about misleading promotion will deter drug promoters who might otherwise violate regulations.

Consumers submitted 116 reports to the program, and 24 of them were received a comprehensive review. In addition, representatives of regulated industry submitted 24 reports, 14 of which were flagged for a comprehensive review. FDA considers the number and diversity of reports submitted to be indications of the program's success, according to the press release.

FDA Commissioner Hamburg started the Bad Ad Program last year by sending a letter to more than 33,000 physicians. In her letter, Hamburg described FDA's efforts to "collaborate with healthcare professionals to address misleading promotion, wherever it occurs."

The Division of Drug Marketing Advertising and Communications (DDMAC) in the Center for Drug Evaluation and Research later created a video and brochure to provide examples of untruthful or misleading promotion. Ads that omit information about a product's risk, promote unapproved product uses, or overstate a product's effectiveness can be considered bad ads, according to DDMAC literature. During the past year, representatives of DDMAC set up exhibits at 15 medical conferences and spoke to doctors about the program. DDMAC also conducted presentations at two US teaching hospitals.

FDA has issued several Warning Letters as a result of the program. The first one was sent in December 2010 to Hill Dermaceuticals about a website promoting the company's Derma-Smoothe/FS (fluocinolone acetonide) for use on infants.

FDA will expand the Bad Ad program by developing a web-based continuing-education program. To continue its outreach to healthcare professionals, FDA will focus additional efforts on students and doctors in the beginning of their practices. FDA also plans to collaborate with medical, pharmacy, and nursing schools to enhance student education. In addition, DDMAC representatives will continue to attend medical trade shows across the country.

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Editors' Picks of Pharmaceutical Science & Technology Innovations

Pharmaceutical companies have ample experience making tablets, which remain the most common dosage form. But despite the industry's accumulated knowledge, problems in the tablet-production process, such as capping and lamination, sometimes occur. Firms can try to avoid these problems with improved tableters and with instruments that help them understand their ingredients' properties. This month's products are intended to aid the manufacture of tablets. A new tablet press from Fette can produce multilayer tablets. Elizabeth-Hata's new machine enables the precise alignment of cores in core tablets. An instrument from Hosokowa provides accurate information about power characteristics, such as flowability.

The PT-X powder-characteristics tester
Hosokawa Micron Powder Systems
www.hmicronpowder.com

Press produces various tablet formats

The FE55 tablet press from Fette Compacting can be configured for traditional monolayer use, monolayer use for direct compression, and double-layer use. When configured for double-layer tablets, the device uses its optional third compression station as a tamping station for the first tablet layer. The machine's design enables it to produce approximately 90% of the most common tablet formats, according to the company.

When configured for bilayer manufacturing, the device's pneumatically-actuated lower roll assembly instantaneously raises the first lower compression roll by as much as 2 mm. This action temporarily increases the hardness of the first tablet layer so that it can withstand the trip through the sampling chute and be weighed. The press reverts to normal operation without requiring operator input. In addition, the machine's feeder assembly uses a single paddle with an inverted-cone shape to enable unrestricted product flow.

FE55 tablet press
Fette Compacting
www.fetteamerica.com

Instrument characterizes particles accurately

The PT-X powder-characteristics tester from Hosokawa uses Carr indices and Kawakita's equation for compressibility to determine the flowability and floodability of dry powders. The unit provides automated vibration and includes an electronically controlled vibration sensor to ensure results' repeatability. The PT-X instrument's feeder was specially designed to maintain reliable sample feeding.

By reducing the amount of operator intervention required, the device helps ensure analytical accuracy and repeatability. Analysis is performed quickly through the machine's user-friendly software, which has multilanguage functionality. Users can perform measurements by recording each test sieve's serial number.

Tablet press enables precision core placement

The new version of the Hata CVX Core Press machine from Elizabeth-Hata enables precision core alignment in core-tableting applications. The CVX series is appropriate for multilayer and custom core-tableting. The press has manual washdown capability to facilitate product changeover.

The new unit allows users to insert an item into a predetermined location in a specific die. The geometry of the transfer cog maintains the item's placement within the die, and the position cannot be changed once it has been set. The device holds cores in position and slowly embeds them into the tablet over 32° of rotation, thus enabling consistent, accurate, and repeatable placement. In addition, the press includes technology for core-coating and time-release solid dosage tablets.

The Hata CVX press includes a portable control kiosk that helps save space. The touch-screen control provides a Windows-based software interface that includes context-sensitive help text to simplify press operation.

Hata CVX
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FDA and Manufacturers Ponder Biosimilars Pathway

Jill Wechsler

Follow-on versions of complex biologics require extensive expertise in product development and regulatory procedures.

FDA is working to develop guidelines for documenting the similarity and interchangeability of copycat versions of biotech therapies, a process that is drawing considerable scrutiny from a broad spectrum of manufacturers. There are a host of thorny issues to resolve related to reference products, interchangeability, labeling, and exclusivity. One area of agreement is that producing biosimilars is vastly more complex and costly than manufacturing conventional generic drugs, and that FDA will require broader testing to license a product as biosimilar or interchangeable. Developing a follow-on biotech therapy will require considerable investment in time, resources, and expertise, running up a tab of some $75–$250 million and typically taking seven to eight years, according to Ameet Mallik, global head of Novartis's Sandoz biopharmaceutical division, during an investor call in May 2011.

Even so, the prospect of biopharmaceuticals capturing a greater share of the global drug market is drawing interest from many pharmaceutical and biotech companies. The worldwide market for biosimilars is projected to grow to $3.7 billion by 2015, up from about $250 million last year, according to Datamonitor. As more biotechnology product patents expire and regulatory authorities clarify requirements, biosimilar development is projected to soar. Leading pharmaceutical companies, such as Novartis and Merck, aim to be major players in the field, and even innovator biotech companies like Amgen are eyeing the follow-on market.

Even though BPCI provides 12 years' exclusivity, the subject is far from settled.

Setting a pathway

FDA officials are under pressure from Congress, government agencies, and payers to develop an abbreviated regulatory pathway for approving biosimilars, as authorized by the Biologics Price Competition and Innovation Act (BPCI), which was approved as part of the Affordable Care Act (ACA) of 2010. The legislation aims to reduce spending on prescription drugs by permitting "highly similar" versions of biotech therapies to come to market based on less-extensive nonclinical and clinical data than was required to approve the original reference drug. Manufacturers talk of marketing biosimilars at discounts of 25–30% off branded products, but reimbursement experts say that prices that are just 10% lower will be able to gain market share, particularly for therapies that have high price tags to start.

BPCI gives FDA the task of establishing a process that will encourage development of biosimilars that meet all standards for product safety, purity, and potency. No "clinically meaningful differences" should exist between the new biologic and the reference product. Both should use the same mechanism of action and have the same route of administration, dosage form, and strength (see sidebar, "Ensuring comparabiliy and similarity"). A biosimilar also has to be manufactured, processed, packaged, and stored in facilities that meet GMP standards.

FDA began the formal guidance-development process for evaluating biosimilars at a November 2010 public meeting. Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), recently indicated that

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In Washington this month

- FDA continues guidance-development process for evaluating biosimilars.
- Generic-drug and innovator companies discuss reference product qualification.
- Legislators and industry debate exclusivity timeframes.

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general guidance should appear before the end of 2011, and that requirements for human testing will vary according to how well a biosimilar can document similarity to the innovator product.

User fees. FDA also is moving forward with a user-fee schedule for biosimilars. The agency proposes to set fees similar to those for innovator drugs and biologics, but will take a new approach to help finance FDA's extensive involvement in steering sponsors through the development process. The plan is for manufacturers to pay a product development fee of $150,000 with submission of an investigational new drug application and annually thereafter; those upfront payments would be subtracted from the eventual application fee. Performance goals for approving applications would apply to applications submitted within two years of the expiration of exclusivity for the reference product, but not to applications for products that have years to wait before they can enter the market.

The application process. Even without final guidance, FDA officials say they're ready to evaluate biosimilar applications on an individual basis. "We were open for business a year ago," said Steven Kozlowski, director of CDER's Office of Biotechnology Products, at the "Future of Biosimilars" conference in May 2011, jointly sponsored by the Drug Information Association (DIA) and the Food and Drug Law Institute (FDLI). So far, no manufacturers have attempted the 351(k) approval route for biosimilars authorized by BPCI and are instead continuing to use established drug-approval procedures for some follow-on versions of proteins. If FDA testing requirements and other policies make the biosimilars pathway too arduous, manufacturers say they may use the traditional biologic license application (BLA) and sidestep the 351(k) route altogether.

In devising guidance, FDA has to tackle some basic issues, such as which products fall under the new regulatory program. BPCI extends the definition of biologics to most proteins beginning in March 2020. That definition raises questions about how the change will affect manufacturers of human growth hormones and other proteins, and how they should proceed during the nine-year transition period.

Reference products. A thorny subject is whether FDA can approve a biosimilar based on a reference product that is approved overseas, but not in the United States. BPCI says that reference products have to be licensed by FDA, but biosimilars manufacturers want flexibility to permit comparison with a biologic licensed by a foreign regulatory body under certain circumstances. This approach is important for global biosimilar-development programs, pointed out John Pakulski, head of US biopharmaceutical regulatory affairs at Sandoz, at the DIA/FDLI conference. If every country or region requires local trials using locally sourced products, he observed, that could undermine efforts to establish a less-costly abbreviated development program.

Pakulski and others propose a science-based approach that permits the use of foreign reference products when they are made by a US manufacturer or in a facility inspected by FDA; licensed in highly regulated markets, such as Europe or Japan; and have a sufficient postmarketing history to confirm safety, purity. and potency. Additional scientific data could be required on a case-by-case basis to establish comparability between a US and foreign-sourced reference product.

Another contentious question is whether biosimilar manufacturers can extrapolate data from a clinical study to other indications of the reference product. European regulatory authorities permit this if the added indication involves the same mechanism of action and same receptor, and if extrapolation of immunogenicity data applies to a lower-risk population or route of administration. Biosimilar-drug sponsors indicate that extrapolation may be appropriate if supported by open-label safety studies for each indication.

Interchangeability issues

A key challenge for FDA is to define interchangeability testing requirements and whether clinical switching studies will be required. Manufacturers want products to qualify as interchangeable because the first follow-on biologic so deemed by FDA enjoys a year of market exclusivity, during which FDA may not approve another similar interchangeable product. The designation also is important for acceptance by patients and healthcare professionals, and for possible substitution by pharmacists and prescribers.

Gordon Johnson, vice-president of the Generic Pharmaceutical Association, noted at the DIA/FDLI meeting that switching studies are not required for innovator manufacturers to document comparability following postapproval changes. Gillian Woollett, chief scientist at the law firm Engel & Novitt, added during the conference that documenting comparability to the innovator inherently supports a finding on interchangeability. Innovator biologics experience batch-to-batch variability over the product's life time, Woollett observed, and that kind of variability should be accepted in biosimilars.

Yet, innovators maintain that clinical studies in multiple populations with different risk–benefit profiles are necessary to document that there are no greater risks of safety problems or efficacy differences with product switching. Amgen Vice-President Anthony Mire-Sluis maintained that head-to-head studies are needed to compare immunogenicity between reference and follow-on biotechnology products, and that different assays can yield different rates of immunogenicity. He also wants product labels to state explicitly the approved indications of a therapy and whether a biosimilar is interchangeable for that use.

The potential for product naming and coding to drive coverage and reimbursement generates heated debate on those topics. Innovator firms maintain that biosimilars should have unique names to distinguish them from reference products, an issue that BPCI failed to address. Different names can ensure traceability of adverse events, reduce confusion about interchangeability, and prevent dispensing errors.

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Ensuring comparability and similarity

The challenge for biosimilars developers is to demonstrate that product quality attributes, molecular structures, and biological and immunochemical functions are similar to those of the reference product, even though they are produced from a different cell line and based on unique processes. Full analytical characterization of biosimilar products is essential to understand the chemical structure, physical properties, impurity profile, and degradation pathways, and to determine the effect of process change on the drug substance.

Complex compound structures and manufacturing processes add to the difficulty in replicating biological products, and different starting materials can yield different impurity profiles, explained Paraxel Vice-President Cecil Nick at the Drug Information Association/Food and Drug Law Institute biosimilars conference in May 2011. To be a biosimilar, a product should have an identical amino-acid sequence, indistinguishable folding, and a similar glycoprofile, and any differences must be justified. While fluctuations in temperature, pH, solvents, and surface interactions can affect protein folding, improved methods can better evaluate compound structure and measure heterogeneity.

One tricky issue for FDA officials and manufacturers is that "drift" in quality attributes of a reference product may cloud the comparability picture. A steady shift in reference-product attributes over time, which can result from changes in materials and modifications in procedures, equipment, or facilities, could affect prior findings of safety and efficacy between the innovator and biosimilar and thereby, raise questions about ongoing interchangeability.

Beyond documenting biosimilarity based on molecular structure and in vitro assays, a demonstration of equivalence will involve nonclinical pharmacology and toxicology studies, as well as pharmacokinetic and pharmacodynamic testing in humans. Additional clinical studies will be needed to document equivalent efficacy in at least one approved indication. Yet, even innovator firms acknowledge that an appropriate biosimilar pathway would involve less extensive animal toxicity testing and reductions in dose finding and Phase II clinical trials. Equivalence and noninferiority trials would use active controls (not placebos) for ethical as well as practical reasons.

Biosimilar advocates prefer names linked to a reference product to "make clear to prescribers and patients that the products are related," explained attorney Erika Lietzan of Covington & Burling during the conference. Some physicians propose unique names only for noninterchangeable biosimilars. European Union guidance calls for biosimilars to have different names, but most relate to innovator products. FDA officials may seek to promote safety with names that differentiate similar versions of a drug.

Product coding raises related issues. Innovators want biosimilars to have their own reimbursement codes, while biosimilars makers want the same code for all drugs in the same class. A dozen human growth hormone products have the same Medicare reimbursement code and thus receive the same rate of reimbursement, explained attorney Laura Loeb of King & Spalding. But even without interchangeability status and common codes, Loeb predicts that it will be difficult for more expensive reference products to maintain market share. Formulary committees and state Medicaid programs, she points out, can drive prescribing through formulary placement, higher copays, prior authorization, and requiring-step therapy procedures for reference products. "The burden will be on the reference product to prove superiority to the biosimilar," Loeb observed, "not the other way around."

Exclusivity

Even though BPCI provides 12 years' exclusivity for innovator biologics, a period when FDA cannot approve a product based on innovator data, the subject is far from settled. Innovators also gain a four-year delay following reference-product licensure during which time biosimilars sponsors cannot submit a 351(k) application. Biotech companies consider these protections crucial for encouraging investment in research and development. Critics, however, claim that 12 years exclusivity is too long, and the Obama administration recently proposed reducing exclusivity to 7 years.

The shorter protection period also aims to minimize exclusivity "evergreening," which refers to the practice of manufacturers seeking an additional period of protection for products that are modified enough to qualify as new. FDA has to define what changes would sufficiently affect a product's safety, purity, or potency to warrant extended exclusivity. The change has to be significant, says Kozlowski of CDER. "I don't think that 'slightly better purity' is enough to extend exclusivity," he observed at the DIA/FDLI conference.

As with conventional generic drugs, patent and exclusivity issues involving biosimilars are likely to generate extensive regulatory maneuvering and lengthy court battles. Manufacturers on both sides of the market are expected to file citizens' petitions challenging FDA's interpretation of BPCI, particularly regarding how it defines "biosimilar" and what constitutes "interchangeability."

The legislation establishes an even more complex system for dealing with patent and regulatory disputes than applies to conventional generic drugs. Unlike the Hatch–Waxman Act, BPCI doesn't directly involve FDA in listing patents. Instead, the law requires biosimilars developers to provide reference-product makers with a full dossier on its process and product so that the innovator can identify those patents it feels may be infringed. This "hokey-pokey process," explained Sidley Austin Attorney Jeffrey Kushan, was designed to promote early agreement on those patents worth fighting about. But Kushan fears it will create a more complicated litigation process involving multiple deadlines and requirements that will please no one. Biosimilars makers complain that too many parties will see their confidential regulatory filings, while BLA-holders stand to lose protection if they fail to follow all the rules. If the 351(k) process becomes too contentious and costly as a result, biosimilars sponsors may opt to follow the traditional BLA route to market, which offers the reward of 12 years' exclusivity. **PT**

IMAGE: STOCKBYTE/GETTY IMAGES

PharmTech.com/bio

Biotech Financing Blues

Tracy T. Lefteroff

The performance of biotechnology venture capital and investment is lackluster at best.

The first-quarter 2011 MoneyTree Report by PwC US and the National Venture Capital Association, which tracks venture-capital financing, presents a case for cautious optimism. The report, based on data from Thomson Reuters, showed modest growth of 5% in terms of dollars invested in the US biotechnology industry on a year-over-year basis. Funding rose to $784 million in the first quarter of 2011, compared with $746 million in the first quarter of 2010. The increase followed a disappointing second half of 2010, when the biotechnology industry slipped into second place behind the software industry in share of venture dollars captured. The increase for the first quarter, although promising, lagged the 13.7% year-over-year growth rate of all sectors combined.

Deal volume presented a somewhat bleaker picture. Compared with the first quarter of 2010, the number of venture-capital deals declined 21% from 107 to 85. The 2011 first-quarter deal volume marked the fewest number of biotechnology deals in a single quarter since the second quarter of 2003. Deal volume for all sectors combined also declined, but the number for biotechnology fell further.

The average biotechnology deal size, however, was a bright spot, up 32% year-over-year to $9.2 million, which outperformed the $8-million average for all industries. On the down side, the biotechnology industry captured only one of the top 10 venture-capital deals in the first quarter—$72 million in early-stage financing for a provider of biotechnology research services.

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Early-stage funding for biotechnology companies declined by 4% year-over-year to $442 million in the first quarter of 2011, but late-stage funding increased by 19% to $342 million. First-time funding dropped dramatically by 44%, but follow-on funding grew 18%. A total of $697 million went into 62 follow-on deals; $88 million went into 23 first-time deals.

The mass exodus from biotechnology that some analysts had feared did not happen.

Fewer deals and smaller deal size are the norm for fledgling companies. Early-stage biotechnology companies may be a decade away from generating revenue. Lengthy and costly research and development and uncertainty in the regulatory approval process continue to drive more investors toward follow-on and later-stage deals with companies that are closer to successful product launches or the exit market.

Overall, the biotechnology industry dropped to third place behind the software and industrial/energy sectors in the dollar amount invested in the first quarter of 2011, but the combined performance of biotechnology and medical devices, the other life-sciences sector, showed continued strength. The mass exodus from biotechnology that some analysts had feared did not happen. Considering the level of capital and time required for drug discovery and development, investors must sharpen their pencils when looking at the potential return of biotechnology investment. Despite the challenges of long lead times to revenue generation and the unpredictability of regulatory approval, investors recognize that demographic trends point to growth potential. The global population is aging, which is expected to lead to higher consumption of pharmaceuticals. Chronic conditions, such as diabetes and heart disease, already epidemic in the US, are rapidly extending into developing countries.

Competition for biotechnology investment dollars remained heated in early 2011. The San Francisco Bay area, New York Metro, Boston, San Diego Metro, and the North Carolina Research Triangle area received the most biotechnology venture-capital dollars during the first quarter of 2011. The San Francisco Bay area captured the highest amount at $248 million, but New York Metro, at $130 million, showed the largest percentage increase.

Exit activity in the biotechnology industry has picked up since the doldrums of 2008 and 2009. Four of the 14 venture-backed initial public offerings (IPOs) during the first quarter of 2011 were from biotechnology companies. Some analysts noted weakening biotechnology demand because most of those companies that went public with venture-backed IPOs this year have seen offering prices below what they had expected. Still, the acceleration in overall IPO activity bodes well.

The biotechnology industry captured only six of the 109 venture-backed mergers and acquisitions (M&A) for the first quarter of 2011. M&A biotechnology deal activity is expected to pick up as the year progresses, and Big Pharma and Big Biotech continue to ferret out deals to infuse their pipelines. Overall, for companies that can develop the right products, especially biologics, to meet the high demand for treatments for cancer and rare diseases, investor interest is expected to remain high. **PT**

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Innovation in Controlled-Release Injectables

Erik Greb and Rich Whitworth

High demand could lead to novel formulations.

Sustained-release injectable biologics are popular among patients who suffer chronic illnesses. Injectable products that offer controlled drug release can reduce the frequency of injections, which makes it easier for patients to remain compliant. Sustained-release injectables also can offer therapeutic advantages and enhance the quality of patients' lives. Demand for these medicines is increasing, and the desire to extend the patents of branded biologics likely will lead to innovations in controlled-release applications.

Polymeric microspheres

One controlled-release technique suitable for biopharmaceuticals is based on polymeric microspheres. In this method, manufacturers use polymers to construct a biodegradable matrix within which a drug can be encapsulated. By choosing polymers with the proper characteristics, and by modifying the matrix properties, manufacturers can establish the desired release profile for the drug. Biodegradable microsphere systems can deliver peptides, proteins, nucleic-acid-based drugs, and even small molecules, says Ramin Darvari, senior principal scientist for novel delivery technologies at Pfizer.

Drugmakers can form the microspheres by creating oil–water emulsions. The process uses an immiscible aqueous–organic solvent system that formulators can design to accommodate various presentations of the drug compound, including aqueous solutions and dry particles. "Although traditional emulsion-based processes rely on exerting high shear on the system to generate the desired particle-size distribution, recent advances in emulsion-based particle-engineering processes have made it possible to achieve more precise control of the particle-size distribution" without the high shear that could denature a therapeutic protein, says Darvari.

Manufacturers must extract solvents such as methylene chloride and ethyl acetate from the emulsion to form the particles and remove the residual solvent through freeze-drying or spray-drying. An alternative approach to avoid solvents is to use hot-melt encapsulation to create microspheres for heat-tolerant molecules.

Manufacturers can choose among various synthetic and natural biodegradable polymers to create injectable microspheres. Most often, formulators opt for synthetic polymers, such as polyesters, poly(orthoesters), polyanhydrides, and polyphosphazenes, says Darvari.

In particular, the poly(lactide-co-glycolide) (PLGA) family of polyester copolymers is used extensively in drug delivery. PLGA might have some undesirable attributes, however. The compound exhibits bulk degradation, rather than surface degradation, which fosters the formation of the polymer's acidic degradation byproducts, lactic acid and glycolic acid. These byproducts, in turn, reduce the pH of the microenvironment within the matrix. This effect might cause drug degradation within the matrix, as well as irritation and discomfort at the site of injection, says Darvari. This problem can be mitigated by adding buffering or neutralizing agents to the formulation, thus allowing PLGA to be used safely and successfully in controlled-release injectables.

The polymeric matrix controls drug release by acting as a diffusion barrier that determines the rate at which the drug payload dissolves. The barrier also controls the rate at which the dissolved payload diffuses from the matrix. Formulators could modify the polymeric matrix to create release mechanisms that range from diffusion-based to degradation-based systems.

The release rate from a microsphere partly depends on the composition of the polymer. For example, the release rate from a PLGA microsphere is affected by the ratio of lactide to glycolide, says Darvari. Molecular weight is an important factor, too. Polymers with high molecular weights generally release their payloads at a slower rate, says Mathew Cherian, director of global research and development for Hospira. The polymers' hydrophilicity, hydrophobicity, particle morphology, and surface charge also can affect the drug's release profile.

Polymeric microsphere systems allow for a broad range of release profiles, including sustained release with zero-order and first-order kinetics, delayed release, and pulsatile release. The polymer composition also can be modified to provide an initial release of drug substance before the delivery rate stabilizes at a lower rate. "The degree of polymerization, and consequently the molecular weight, modulates the release rate," says Cherian. "By using two or more molecular-weight ranges in separate steps, during formulation, multiple release rates can be obtained."

The most common goal, especially for treating chronic diseases, is a con-

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stant- or sustained-release profile. Polymeric microspheres can provide sustained drug release for one week, or for as long as a month. Some companies are developing products with release profiles of three months or more. Life-science company Peptron has a three-month formulation of leuprolide in clinical trials. Eligard (leuprolide) from Atrix Laboratories has a three-month profile. Debiopharm has a triptorelin-embonate formulation capable of delivering for as long as six months.

In addition to the wide range of release profiles that they enable, polymeric microspheres have other advantages. The synthetic polymers can be readily synthesized in a narrow range of properties (e.g., molecular weight, viscosity, and comonomer ratio). Then the classification and adherence to standards could be reliably achieved by common methods of analysis.

PLGA polymers also are nonimmunogenic. Because they eventually degrade to their original monomeric components, the microsphere can act as an injectable depot system without the need for removing the matrix once the depot is depleted.

Particle replication in nonwetting templates is based on technologies used to make transistors.

Microspheres also can enhance the safety of potent drugs by preventing an initial dosage spike upon administration. By encapsulating the drug and controlling its release, microspheres avoid the spike in blood levels seen after the injection of unencapsulated drugs.

The PRINT technique

The pharmaceutical industry has frequently benefited from technologies developed in other industries. The method called Particle Replication in Nonwetting Templates (PRINT), which is based on technologies used to make transistors for the computer industry, potentially could be applied to making controlled-release injectable drugs. A team led by Joseph DeSimone, a chemistry professor at the University of North Carolina at Chapel Hill, developed PRINT, which gives companies increased control of the size and shape of drug particles.

In this technique, scientists pour a drug solution into a template that forms particles with the desired dimensions and form. The solution is sometimes formulated with surfactants or lipids, and the resulting particles are colloids that are either stabilized sterically (e.g., through the incorporation of polyethylene glycol) or electrostatically (i.e., though a charge), says DeSimone. Formulators disperse these particles in phosphate buffer.

When an emulsion is used to create PLGA microspheres, a fraction of the

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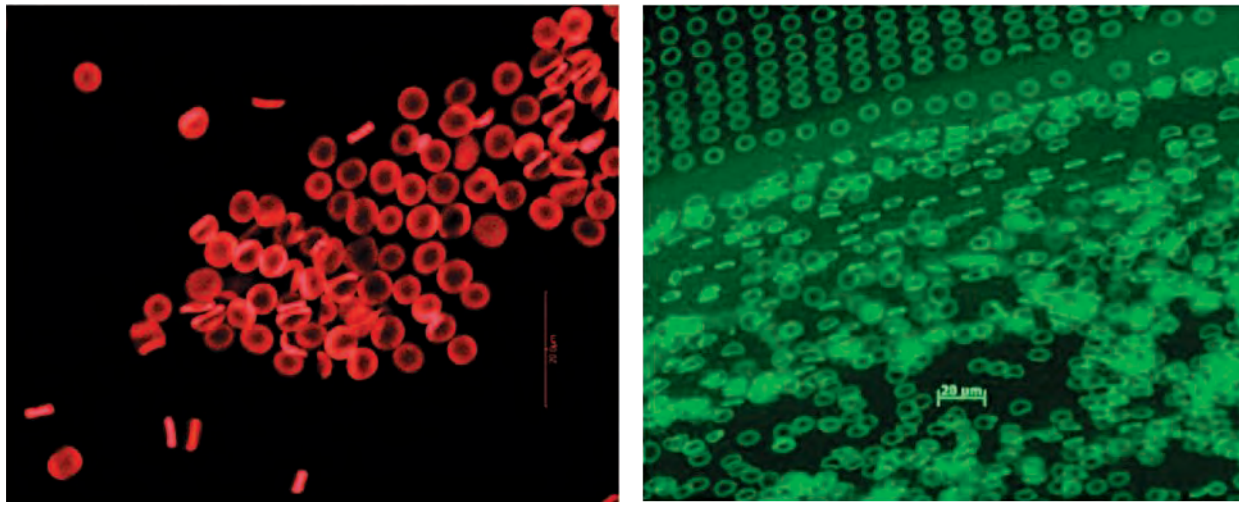
Particle replication in nonwetting templates can produce shapes that mimic (left) red blood cells and (right) metastatic cancer cells.



drug usually separates into the polymer, thus trapping it and preventing it from being released. The amount of drug loaded into PLGA microspheres is consequently limited because it is difficult to control partition coefficients. In contrast, the PRINT technique enables manufacturers to make PLGA particles that contain 40% drug. "That's three or four times higher than anyone in the literature has been able to achieve," says DeSimone.

One way that scientists can control drug release from a PRINT particle is by using degradable polymers, such as PLGA, as the particle matrix. The polymer's properties can be exploited or modified to achieve the desired release profile. The electrostatic interactions and the solubility characteristics between the particle matrix and the drug cargo that it contains can be adjusted. The more similar the polymer's characteristics are to those of the drug, the higher solubility the drug will have in the polymer. Another method would be to incorporate prodrugs into the PRINT particles. Formulators choose prodrug linkers with the appropriate rates of degradation to ensure that the drug is released from the carriers at the desired rate.

Particle size and shape also can affect a drug's release rate because different sizes and shapes have different surface-area-to-volume ratios. "Generally, if one has a set volume of particle, decreasing particle size will increase the available surface area for water contact, and thus increase the release rate," says DeSimone. Shapes, such as spheres, which minimize surface area to volume, have decreased drug-release rates, he adds. Through the PRINT technique, surface-area-to-volume ratios can be adjusted to achieve the required release rate for the product.

PRINT also can help extend a drug carrier's elimination half life, thus keeping it in the body longer (1). The more deformable a drug particle is, the more easily it can bypass biological barriers such as the lung and spleen, and the longer its elimination half-life. Rigid particles tend to get stuck in small capillaries.

DeSimone's team made particles that were 1.5 µm thick and 6 µm in diameter to mimic the properties of red blood cells. "We systematically varied the degree of deformability. When we matched the degree of deformability of a red blood cell, we had a 30-fold increase in elimination half life. We had a four-day elimination half-life for a 6-µm diameter particle, which is really unheard of," says DeSimone.

Because the PRINT technique offers enhanced control over particle properties, including size, shape, chemistry, and surface area, it could enable a wider range of release rates for injectable drugs compared with manufacturing techniques, such as emulsions, says DeSimone. The method also allows manufacturers to load particles with more types of drugs than other techniques do, including hydrophilic, hydrophobic, and biomacromolecules. He adds that PRINT can modify the particle matrix easily, thus establishing the desired release profile. "The precise control over numerous particle parameters is what makes PRINT so versatile," says DeSimone.

Solid-dose injection

Several options for controlled-release injectable dosage forms, though effective, require somewhat complicated formulations that present unique manufacturing challenges. Injectable controlled-release drugs are traditionally in liquid form because of the constraints of the standard needle-and-syringe delivery method, which limits formulation options.

The ability to retain a solid formulation offers several advantages, not least in terms of stability. The injection of solid doses is not a new concept; drug implants have been around for some time. AstraZeneca's Zoladex (goserelin), for example, was introduced more than 20 years ago. Used to treat prostate cancer, the 10.8-mg implant must be injected by a healthcare professional through a 14-gauge needle with an aseptic technique. "Not particularly pleasant," says Charles Potter, chief technical officer at specialty pharmaceutical company Glide Pharma. However, the formulation does offer sustained release over a 12-week period and makes such injections relatively infrequent.

IMAGES ARE COURTESY OF JOSEPH DESIMONE AND TIMOTHY MERKEL OF THE UNIVERSITY OF NORTH CAROLINA

Taking the idea of an implant one step further, Potter asked, "Why not use the drug as the needle? If the formulation can be made solid enough, it can be formed into a sharp point." That premise is the basis of Glide Pharma's Solid Dose Injector (SDI) technology, which uses a solid, homogenous mixture of drug and excipient.

In controlled-release formulations, the excipients used are biodegradable polymeric compounds, such as PLGA or polyethylene glycol, that are compatible with the Glide implant manufacturing process. By blending various grades of polymer, changing the ratio of drug to polymer, and manipulating process conditions, varied release profiles can be created with Glide formulations. On the other hand, if immediate release is required, the formulation would require quick-dissolving excipients, such as a single sugar or a blend of sugars that provide the physical strength required, but dissolve within seconds in the tissue. And although other excipients may be required to increase stability, such as for thermally labile biological macromolecules, formulations remain relatively simple.

The manufacturing process for the solid dosage form is also simple: the active ingredient and a blend of selected excipients are mixed together and passed through a standard twin-screw extruder, usually at room temperature to ensure that the active ingredient is not damaged. The spaghetti-like extrudate is then cut into individual doses that are pointed at one end and flat at the other. The drug implant is loaded into a sterile cassette and pushed directly into the tissue using a simple, reusable spring-driven actuator. The rate of degradation of the polymeric matrix within the tissue controls the release of the drug.

Potent drugs are good candidates for the company's solid-dose injection technology because they are administered in small doses that can be delivered easily as small implants. Beyond dosage size, Glide's technology does not seem limited by drug type. "We've got some very exciting vaccine data where we've shown the potential for better efficacy than a needle and syringe, and we've worked with several peptides and proteins," says Potter.

Looking to the future, Potter sees a potential market in the treatment of Type II diabetes because of Glide SDI's suitability to self-administered drugs. "Type II diabetics need a basal layer of insulin across the day. We can address Type II diabetes with our system, but different people need different levels, so we would need several dose levels for our formulations."

Conclusion

Scientists are refining current technologies and developing new means of controlling the release of injectable drugs. Patients seem likely to benefit from further innovations.

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The Power of Particle Characterization

Stephanie Sutton

How pharma's drive for manufacturing efficiency has bolstered interest in and technologies for particle characterization.

Particle-characterization data is central to the development, manufacture, and quality control of pharmaceutical products. The characteristics of a pharmaceutical's composite particles can affect the product in many ways, including by influencing drug efficacy and stability, as well as how the product behaves during processing. When considering the importance of particle characterization, the International Conference on Harmonization's (ICH) Q6A guideline on specifications (1) is a useful starting point because it identifies potentially important particle variables, including polymorphic form, enantiomeric purity, and particle size and distribution. The guideline also provides a decision tree to help determine when related testing is required.

Historically, industry has paid greater attention to control of particle size and distribution, which, according to ICH Q6A, can significantly affect the dissolution rates, bioavailability, and stability of drug substances in both solid and suspension products. Today, particle characteristics are attracting even greater focus as industry strives to increase manufacturing efficiencies. This drive has been largely influenced by the growing emphasis on quality by design (QbD), which encourages pharmaceutical companies to use an information- and risk-based approach to optimize product development and manufacture. Using particle characterization to understand how a product behaves during processing supports this initiative.

This article takes a brief look at what factors have driven innovations in particle-characterization techniques and how technology may advance in this area in the coming years.

Innovations in particle characterization

Two of the earliest particle-sizing techniques were manual microscopy and sieving. These methods are still used today, but both have drawbacks. For instance, microscopy is slow and manually intensive, while sieving is unsuitable for fine or cohesive materials. As such, industry has sought more advanced particle-sizing techniques.

One such approach that is gaining popularity is laser diffraction. "Although laser diffraction methods have been used for the last 30 years, continuous development has resulted in much more accurate and reproducible measurements between manufacturers," explains Graham Rideal, founder of and a senior scientist at Whitehouse Scientific, which specializes in particle-sizing methods.

Paul Kippax, product group manager at Malvern Instruments, a producer of analytical equipment, agrees that laser diffraction is an important technology, particularly because its measurement range (0.1 to 3000 μ) covers the vast majority of particle-sizing applications used by industry. In addition, laser diffraction is capable of high-speed size distribution sampling (typically less than 20 s, according to Kippax), is nondestructive, and is suitable for automation. "Today's laboratory laser diffraction analyzers have been automated to the point of push-button operation, with sample loading being the only remaining routine manual task," says Kippax.

Imaging and microscopy are not being left behind, however. Some recent advances have been made with these analytical techniques. "The continuous and concomitant development of imaging technology and high-speed computers has transformed the humble microscope from a predominantly qualitative instrument into one of the most potent quantitative tools available today," explains Rideal. "This development has extended the definition of a particle from that of a simple equivalent spherical diameter into a comprehensive shape analysis where length, width, and perimeter can be measured at tremendous speeds."

Indeed, during the past few years, industry has placed a growing emphasis on particle characteristics other than size, such as shape, surface charge, and roughness. "Particle sizing is just one element of particle characterization," says Rideal. "Other disciplines in this sector include particle shape, flow properties, both in the dry state and as suspensions (rheology), morphology—including crystal structure, and porosity. Particle sizing alone is therefore not always the sole answer to efficacy.... A combination of physical properties is invariably investigated in arriving at the final solution."

According to Kippax, particle shape, in particular, has become an important parameter for both processing and final product quality. "In direct compression tableting, for example, shape is known to have an impact on blend uniformity, the consistency of powder flow through the press, compressibility, and the mechanical strength of the finished tablet," he says. "On the imaging front, many are also already looking beyond shape to composition."

Process development

Understanding particle characteristics can benefit process development in several ways. The latest technologies, such as the on-line laser-diffraction systems noted above, enable processes to be monitored in real time during development work, which provides better control and facilitates scale up. "The sector's interest in on-line, real-time measurement has risen sharply as it

IMAGE: INFLUX PRODUCTIONS, PHOTODISK, GETTY IMAGES

works toward greater manufacturing efficiency," says Kippax. "Real-time monitoring accelerates the reliable identification of 'cause and effect' during process development and has a valuable role to play in the transition to smarter operation."

Real-time monitoring, however, is not yet available in all areas of particle characterization. Tim Freeman, director of operations at Freeman Technology, which specializes in powder characterization, adds, "I would perhaps highlight particle shape analysis—automated imaging—as a prime example of a technique with proven applicability, that would be a desirable addition to the real-time selection for pharma, but has yet to make this transition."

Another way that particle characterization can benefit process development is through simulation, which involves using characterization data to construct mathematical models that predict process performance. These models, if robust, can be used to conduct virtual experiments.

"The big attraction of process simulation is that it allows virtual experimentation, which is cheaper and quicker than the laboratory or pilot scale equivalent," explains Kippax. "The drawback is the effort required to develop a reliable model." Despite this, however, Kippax added that he expects process simulation to become more widely used within in the industry in the coming years because of the potential it has for aiding scale up and troubleshooting.

Future advances

Particle characterization has come a long way from its early days, but there is always room for more progress. "The next major development in particle sizing is likely to be in measuring in three dimensions," says Rideal. "Computer technology will be a driving force where the current impressive computer graphics from the film industry will be incorporated into particle sizing. There is also a move to borrow technology from the medical world, so expect to see X-ray CAT scans and MRI instruments appearing in the particle-metrology laboratory."

Meanwhile, Kippax is hopeful that there will be more advances in laser diffraction. "One goal is to make the performance gains already made more universally accessible. Greater embedded support during method development and throughout the measurement process, for example, would ensure that even inexperienced users could fully exploit the technology."

With such improvements on the horizon, industry's main challenge may not stem from technology, but rather from the skill of the operator using it. "Just because an instrument costs in excess of $100000 does not mean that the results are any better than using a sieve costing £100," says Rideal. "The old adage of 'rubbish in, rubbish out' has never been so relevant."

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For an expanded version of this article including information on inhaled pharmaceuticals and powder characterization, visit PharmTech.com.

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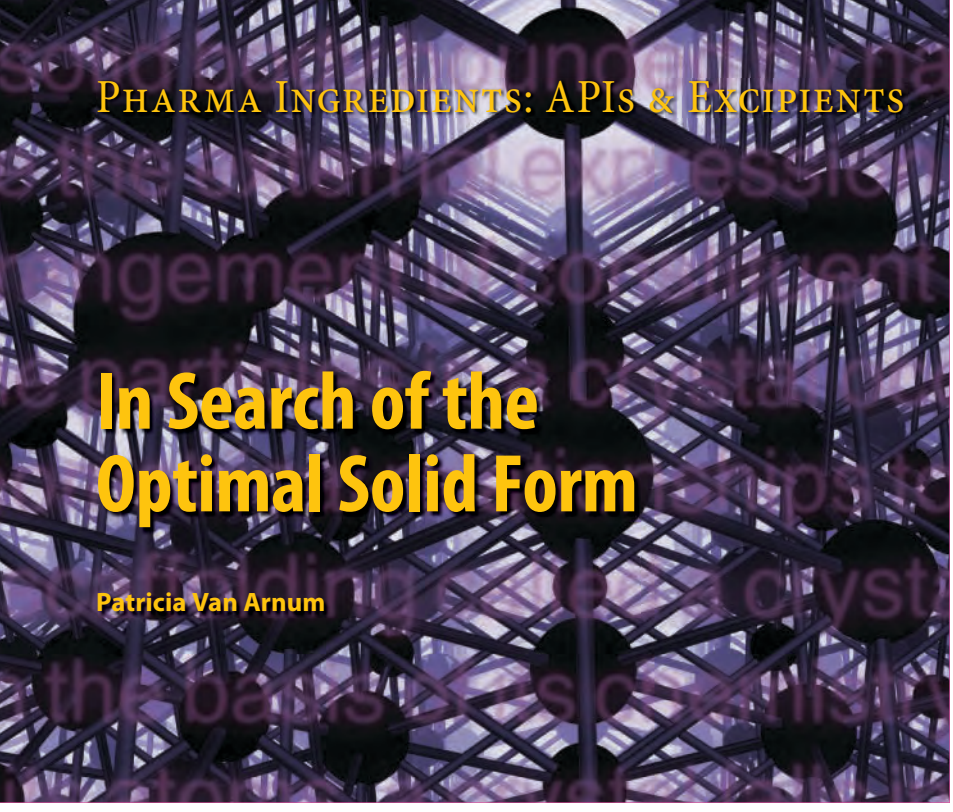


In Search of the Optimal Solid Form

Patricia Van Arnum

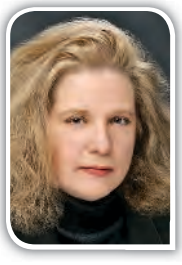
The solid form of an API plays a crucial role in drug quality, and advancing methods for screening, detection, and characterization is key.

The solid form of an active pharmaceutical ingredient (API) influences the drug's solubility, stability, and compatibility with other components in a formulation. API manufacturers are tasked with screening, detecting, and characterizing various physical forms, such as polymorphs, solvates, amorphous materials, and partially disordered materials. Applying solid-state chemistry, however, can be a time-consuming and difficult job, and several recent developments point to ways to facilitate the search for the optimal solid form.

The task at hand

"It is important to apply the most appropriate means of characterizing or identifying all physical forms," says Seenu Srinivasan, PhD, global vice-president and chief scientific officer of CMC pharmaceutical development services at Covance. "On choosing the preferred physical form, a robust crystallization or preparation process needs to be developed, preferably using solvents that are safe, available in large quantities, and are environmentally friendly. Generally, the thermodynamically most stable form is preferred for development. However, in some cases, it may be necessary to progress metastable crystalline forms, solvates, hydrates, or even amorphous materials."

He adds that co-crystals, where more than one molecular entity is incorporated into the crystalline unit cell, can be considered as well. "The latter approach is useful for pharmaceutically engineering the properties of a drug substance when no ionizable moieties are present in the parent molecule," he says. Even when the product is not administered as a solid dose, the physical form of the drug substance should be characterized as fully as possible to ensure that there is no interbatch variability, which may in turn affect, for example, reconstitution time or chemical stability. "We have seen many examples where very subtle variations in physical properties of different batches of an API can have profound effects on its behavior," he says.



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Decisions to be made

The optimal physical form is based on several factors, which may be influenced by the target product profile, including bioavailability, physical and chemical stability, desired dissolution properties, the impurity profile of the API, drug-substance hygroscopicity, morphology, size distribution, compaction properties, and ability to formulate. "The higher ranking of these criteria for a particular API is used in the decision to choose a free molecule, salt form, or co-crystal," explains Laurent Lafferrere, PhD, head of CMC development services in Porcheville, France, at Covance.

Identifying polymorphs, where a drug substance exists in two or more crystalline phases, is crucial. Polymorph stability is evaluated experimentally by monitoring the phase transition of the different polymorphs in different crystallization media and at different temperatures by using *in-situ* monitoring probes and analytical solid-state methods, explains Lafferrere. These data are used to manufacture the desired polymorph and to control it through the various manufacturing steps. Polymorphs can undergo phase transitions when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray drying, and compaction. Exposure to environmental conditions, such as humidity and temperature, also can induce polymorph transition. The extent of transition depends on the relative stability of the polymorphs, kinetic barriers to phase transition, and applied stress.

The physical stability of polymorphs may be monotropic or enantiotropic, where the relative thermodynamic stability between the two forms can be inverted with temperature. Additional considerations are made when the physical form of the drug-substance may be modified in the formulation process, such as in hot-melt, lyophilization, solubilization, or suspension in a semisolid matrix, says Lafferrere. Also, drug substance–excipient interactions are considered when stabilizing particular physical and other process parameters that may affect the performance or quality of the final product.

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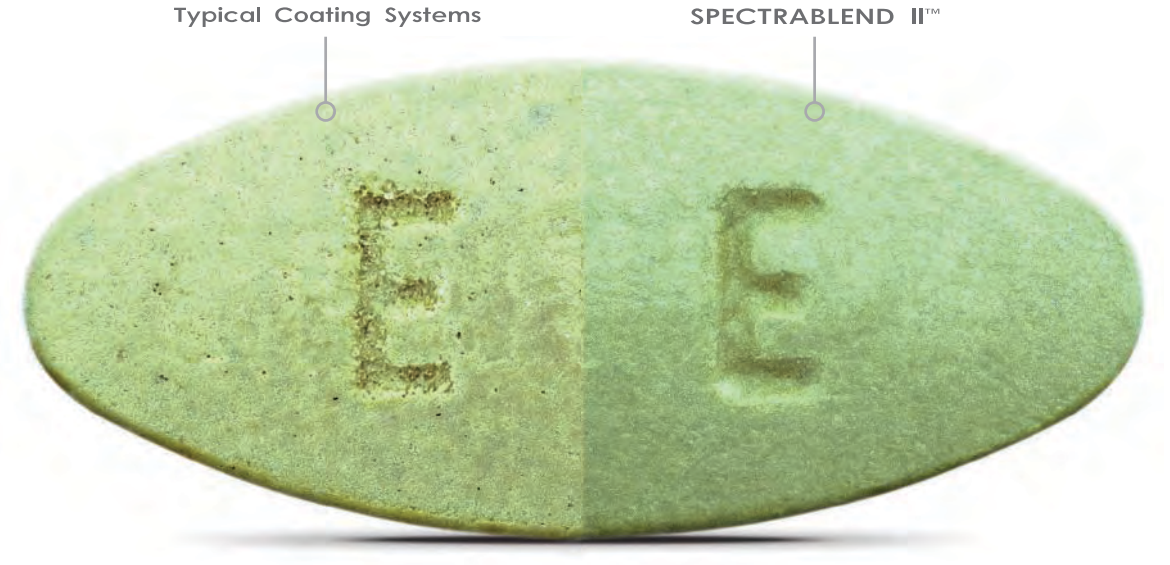

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Screening and characterization

Screening protocols involve recrystallization from a diverse array of solvents under thermodynamically and kinetically controlled conditions, explains Steven Byard, PhD, head of physical and molecular characterization at Alnwick, United Kingdom, at Covance. The transformation of metastable states and extended solvent-based studies conducted under a range of crystallization conditions, such different concentrations, temperatures, cooling rates, and stirring rates, are examined. The effect of different impurity profiles and seeding experiments are further considered.

"Of course, one should never forget that one of the principal criteria for recrystallization may be to obtain a desired target purity, with control over both the impurity profile and residual solvents, in addition to obtaining a defined physical quality. Under some circumstances, we apply controlled stress to the API in a variety of carefully chosen matrices to afford physical forms not normally readily obtained by other means," says Byard.

As development progresses to Phases II and III, there is an increased emphasis on the most appropriate crystal morphology, crystal quality, and crystal-size distribution for the commercial formulation and also definition of specifications for the physical quality of API, explains Byard. Verification

Formulation development forum: controlled agglomeration for poorly soluble drugs

Improving the solubility of poorly soluble drugs is an ongoing challenge. Dispersing a poorly soluble compound in a polymeric matrix to improve solubility and therefore bioavailability is one strategy. To produce the solid solutions or solid dispersions, various methods can be used, such as hot-melt extrusion, spray-drying, melt congelation, and nanocrystal technology (1). LifeCycle Pharma, a technology spinoff from the Danish pharmaceutical company H. Lundbeck, uses a proprietary process, MeltDose, based on controlled agglomeration, to address the problem of poorly soluble drugs.

"Several technologies have been launched to deal with poorly soluble drugs," explains Peter Nielsen, executive vice-president of pharmaceutical development and CMC at LifeCycle Pharma. "Some technologies manipulate the particle size of the active pharmaceutical ingredient (API), and others influence dissolution rate. We see MeltDose as a technology that achieves all these improvements within the same technology."

Nielsen explains the company's approach. A low water-soluble drug substance is dissolved in a vehicle system that is optimized for each drug substance. The drug substance is spray-dried on an inert particulate carrier using fluid-bed equipment and solidified when disposed on the carrier. The carrier captures the active drug in a nanocrystalline or microcrystalline state or as an amorphous solid dispersion. This step is followed by agglomeration that is controlled by optimizing temperature and feed rate to produce the granules, which are directly compressed into tablets. Once in tablet form, the dissolution profile and particle size remain stable.

The selection of the vehicle to match the physiochemical properties of the API is an important consideration in the process. "In some formulations, the API will be present as an amorphous solid dispersion, such as in hot-melt extrusion and spray drying, but in other formulations, the API will be present as crystals in nanometer or micrometer size, resembling nanoproducts more," says Nielsen.

MeltDose, the proprietary process that LifeCycle Pharma has developed, centers on the controlled agglomeration process. "The controlled agglomeration process has some similarities to fluid-bed granulation," says Nielsen. Controlled agglomeration involves placing solid carrier particles in a conventional fluid bed, unto which a liquefied vehicle containing the API is sprayed. When the liquid vehicle is cooled down on the carrier, it agglomerates and forms granules. The controlled agglomeration process is water-free, and in contrast to conventional fluid-bed granulation, uses liquefied (i.e., melted) polymers as the polymeric vehicle. The polymeric vehicle is melted in a specially designed heated melt unit that controls temperature and pressure of the melted vehicle, which passes from the melt unit to a specially designed spray nozzle in the fluid bed, say Nielsen. The produced granules are compressed to tablets using conventional tablet presses.

The polymer vehicles used in the MeltDose process can include a range of hydrophilic and lipophilic materials and are selected for their solubility-enhancing properties and compatibility with subsequent processing steps. Examples of vehicle systems are solid or semisolid polymers with a melting point between 40 and 80 °C, such as polyethylene glycol 6000, poloxamers, and various types of gelucires. The resulting granule size varies with the choice of excipients and lies typically in the range of 200 to 500 µm, says Nielsen.

The vehicle temperature, the spray rate, the atomizing air volume, and product temperature all are important process parameters to consider during the controlled agglomeration step. Also, the addition of different surfactants can result in different sizes of API crystals in the granule (2).

Fenofibrate, a lipid-regulating agent to control cholesterol and marketed as Fenoglide in the United States by Shore Therapeutics, was the first product approved in the US using the MeltDose technology. Fenofibrate was initially approved by FDA in 1993 and later developed by LifeCycle Pharma using the MeltDose process in the formulation. LifeCycle Pharma received FDA approval for Fenoglide to treat hyperlipidemia and mixed dyslipidemia and hypertriglyceridemia in 2007. Sciele Pharma commercialized the product in the US and was subsequently acquired by Shionogi in 2008. In 2010, Shionogi Pharma terminated its Fenoglide North American commercialization agreement with LifeCycle Pharma , transferring commercial rights to Shore Therapeutics.

LifeCycle Pharma is working on other formulations that use the MeltDose process. The company has developed a once-daily modified-release formulation of tacrolimus, a poorly soluble compound with a water solubility of 4–12 µg/m, and the same API as in Astellas's Prograf, an immunosuppression drug used in kidney and liver transplants. LifeCycle Pharma has developed an amorphous solid-dispersion formulation of tacrolimus. The API was dissolved in a melted vehicle at elevated temperature. The solution was sprayed onto an inert carrier in a fluid bed. The resulting granulate was blended with a disintegrant and lubricant and compressed into tablets. The modified-release tablet formulation using the MeltDose technology was developed and tested in humans and is currently in late Phase III testing for the prevention of organ rejection with kidney transplants. LifeCycle Pharma expects to file for regulatory approval for the product, LCP-Tacro, in the US and European Union in the first quarter of 2013.

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that the correct polymorph will be retained in later stages of drug-product development is completed by performing a new polymorph screening with a batch of API from the final commercial synthesis route. The critical manufacturing process variables and their ranges are determined and controlled to produce a robust API process that meets established quality attributes.

Screening for physical forms takes into account properties of the molecular structure and explores the effects of solvents, temperature, concentration and various other parameters that can influence crystallization, explains Byard. Many solid forms are generated by the different crystallization approaches, based on the effect of the interfacial energy between the nucleus and the crystallization media, supersaturation (a driving force of crystallization), and temperature. The crystallization methods can be broadly classified into four groups: crystallization by sublimation, melt crystallization, crystallization by spray drying, and crystallization from solution, which is the most commonly used method because it provides data for the crystallization process development. High-throughput screening methods can be used to cover a wide range of conditions to help ensure that all different forms are recognized.

Many complementary techniques exist for characterizing solid forms, such as single crystal X-ray diffraction, X-ray powder diffraction, solid-state nuclear magnetic resonance (SSNMR), infrared spectroscopy, Raman spectroscopy, Terahertz spectroscopy, hot-stage optical microscopy, and thermal analyses. These methods are routinely used and provide the platforms for incremental improvements.

Recent advances

SSNMR probes samples directly at the molecular level to provide information about structure and mobility. Consequently, the physical form of constituents in either physical or chemical mixtures can be examined with relative ease. "This makes SSNMR a technique of choice for studying drug products, where the physical form of the active can be determined in a complex matrix, even if multiple components are amorphous," says Srinivasan. For example, the presence of physical impurities can be determined when lattice modifications are not altered significantly and, by implication, not readily detected by X-ray powder diffraction (1). In another example, researchers at GlaxoSmithKline reported on SSNMR experiments based on dipolar correlation, spin diffusion, and relaxation measurements to characterize the structure of amorphous solid dispersions (2).

NMR crystallography, which incorporates density functional theory calculations, is used to provide molecular-level information about structure and dynamics of drug substances, including solvate characteristics (3, 4). Recently, X-ray photoelectron spectroscopy (XPS), in conjunction with SSNMR and density functional theory prediction, was used to determine co-crystal formation (5, 6). "This too is a promising approach to understanding exactly what is happening at the molecular level and, by implication, enabling a sound basis for making decisions about formulation processes," says Srinivasan.

Surface properties and the related methods for characterization also are important considerations. Researchers at the University of Manchester and Sanofi recently reported on using a surface-sensitive technique, XPS, in detecting the free-base surface enrichment of a pharmaceutical fumarate salt . They reported that a yellow discoloration was observed at the surface of normally white crystals of the fumarate salt, which was preliminary attributed to the presence of trace amounts of free base. The samples with yellow surfaces could not be successfully milled, which was an important part of the production process for providing material of the required physical quality for product formulation. Because no conventional bulk analytical technique could readily provide an explanation for the yellow color, the researchers used XPS to characterize the salt. The identification of residual free base at the surface of the crystalline material by XPS was significant for optimizing the crystallization process to yield material of required quality for milling at the plant scale (7).

Crystal-structure prediction is an active area of research. "Ab initio crystal structure prediction is another promising area as is elucidating hydrogen bonding potential to provide information about the possibility of discovering additional polymorphic forms of a drug substance," says Srinivasan.

Other approaches

Researchers at the University of Missouri recently reported on a new method for converting drugs from one crystalline form to another by applying gas-induced transformations of the antibiotic clarithromycin and lansoprazole, the API in the gastrointestinal drug Prevacid.

For clarithromycin, the researchers converted the kinetic solvent and guest-free crystal forms to the commercially thermodynamically stable polymorph with a reduction in energy costs relative to other commonly used methods. Typical methods involve desolvation of the initial form to a second form, which is heated for 18 h at 110 °C to finally produce the desired polymorph. In the gas-induced process, the clarithromycin crystals were pressurized with carbon dioxide at 350 psi for direct conversion of the initial form to the final thermodynamically stable form in 4 h. For lansoprazole, the researchers also used carbon dioxide to convert the ethanol hydrate of lansoprazole to the solvent-free form that is used commercially. This process improved the approach used in synthesizing lansoprazole, which involves a solvate that readily decomposes and is stirred in water, filtered, and dried intensively (8, 9).

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The Influence of Hydro-Alcoholic Media on Drug Release

From Polyethylene Oxide Extended-Release Matrix Tablets

Dasha Palmer, Marina Levina, Thomas P. Farrell, and Ali R. Rajabi-Siahboomi

Hydrophilic matrices are widely used for extended release (ER) drug delivery, and polyethylene oxide (PEO) has recently been studied as a matrix-forming polymer. Concomitant alcoholic beverage ingestion may modify the release characteristics of ER formulations, causing dose dumping, which may threaten patient safety. FDA recommends that ER medicinal products should be tested during development to ensure dosage form robustness in hydro-alcoholic media. The authors investigate the influence of hydro-alcoholic media on hydration and drug release from PEO ER matrices using two model active pharmaceutical ingredients with different solubilities in water. No matrix failure was recorded for either formulation when exposed to ethanol–water solutions. In addition, pure PEO compacts made of three viscosity grades of polymer showed consistent swelling upon exposure to hydro-alcoholic media.

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Hydrophilic matrices are a popular and extensively used strategy for oral extended-release (ER) drug delivery. Hypromellose (hydroxypropyl methylcellulose, HPMC) is the polymer of choice as the rate-controlling carrier (1). In addition to HPMC, polyethylene oxide (PEO) has been used as a matrix-forming polymer (2, 3). These excipients are nontoxic and have pH-independent hydration and swelling, good compressibility and lubricity, and versatility due to a wide range of molecular weights. PEO polymers have global regulatory acceptance and can be utilized for modulating the release of drugs at various solubilities and doses (1–13).

PEO polymers are white, free-flowing hydrophilic powders commercially available as Polyox (Dow Chemical Company), water soluble resins (WSRs), with molecular weight ranging from 100,000 Da to 7,000,000 Da (14). A list of Polyox grades suitable for ER hydrophilic matrix applications is shown in Table I.

When in contact with water, PEO hydrates rapidly, swells to a large extent and forms a gelatinous barrier layer around the tablet (15). Drug release from the PEO matrices is generally controlled by diffusion of the drug through the swollen gel at the surface of the tablet and/or gel erosion (9, 16). The rates of wetting, swelling and erosion are controlled by polymer molecular weight and other ingredients within the matrix (17).

Rapid polymer hydration and uniform gel formation are critical to the performance of hydrophilic matrix systems (18). It is also crucial to take into account the type of dissolution media the tablets are exposed to, because it may affect polymer hydration and gel formation.

Alcoholic beverages have been consumed for thousands of years, and a United Kingdom National Health Service survey indicated that 73% of men and 57% of women (aged 16 and over) had alcoholic drinks on at least one day per week (19). In another report, US statistical data showed that around 50% of the American population routinely consumed alcoholic beverages (20).

The potential effect of alcoholic drinks in significantly accelerating drug release from ER oral formulations has been of some concern (21). It is known that alcohol has an influence on the absorption, metabolism and excretion of drugs, which can potentially lead to adverse side effects (22). Toxicity is most often associated with acute intake rather than longer-term consumption of alcohol, but both patterns can impact the toxico-kinetics of concomitantly administered medicines (23).

ER formulations, which are intended for once or twice daily administration, are designed with a higher unit dose of the drug than conventional formulations. Therefore, it is imperative that retardation properties are tightly controlled to ensure that a rapid release of the drug, or dose dumping, cannot occur.

In July 2005, FDA published an alert for healthcare professionals regarding the negative effect of alcoholic drinks on drug release from Palladone (hydromorphone). Alcohol breaks down the ER formulation, and, as a result, increases peak plasma concentration causing potentially lethal dose dumping (24). Several publications have outlined the influence of hydro-alcoholic media on the performance of solid oral ER systems in the years since the FDA alert.

According to Fadda et al., vulnerable formulations are likely to cause adverse pharmacokinetic and therapeutic outcomes in patients on exposure to alcoholic solutions. The extent of the adverse reaction depends on the drug, polymer, and excipients in the formulation (25, 26). Some oral ER dosage forms contain drugs and excipients that exhibit a higher solubility in aqueous solutions containing ethanol. Accordingly, such products may be expected to exhibit more rapid drug dissolution and release in the presence of ingested ethanol (27).

Koziara et al. reported an increased permeability, elasticity, and swelling of cellulose acetate semipermeable

Table I: Polyox WSR NF polymers for ER matrix applications. (Data adapted with permission from The Dow Chemical Company).

Polyox NF Products	Approximate molecular weight (Da)	Viscosity range in water at 25 °C (mPa·s)		
		5% solution	2% solution	1% solution
WSR N-1105 LEO	900,000	8,800 – 17,600		
WSR N-12K	1,000,000		400 – 800	
WSR N-60K	2,000,000		2,000 – 4,000	
WSR-301 LEO	4,000,000			1,650 – 5,500
WSR Coagulant	5,000,000			5,500 – 7,500
WSR-303 LEO	7,000,000			7,500 – 10,000

Note: WSR is water soluble resin. LEO is low ethylene oxide.

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Table II: Polyethylene oxide extended-release formulations used in the study.

Material (Grade, Supplier)	Gliclazide formulation		Metformin HCl formulation	
	% w/w	mg/tablet	% w/w	mg/tablet
Gliclazide (Kemprotec)	15.0	30		
Metformin HCl (Ferico Labs)			50.0	500
PEO (Polyox WSR 1105, Dow)	35.0	70		
PEO (Polyox WSR 301, Dow)			30.0	300
MCC (Microcel 102, Blanver)	49.0	98	19.0	190
Fumed silica (Aerosil 200, Degussa)	0.5	1	0.5	5
Magnesium stearate (Peter Greven)	0.5	1	0.5	5
Total	100.0	200	100.0	1000

Note: MCC is microcrystalline cellulose. PEO is polyethylene oxide.

Table III: Solubility of the drugs, polymer and filler used in the study, in water and alcohol (14, 33–37).

Material	Solubility in water	Solubility in alcohol
Gliclazide	Practically insoluble (<0.1 mg/mL)	Slightly soluble (1-10 mg/mL)
Metformin HCl	Freely soluble (500 mg/mL)	Slightly soluble (10 mg/mL)
PEO	Soluble (33-100 mg/mL)	Insoluble (<0.1 mg/mL)
MCC	Practically insoluble (<0.1 mg/mL)	Practically insoluble (<0.1 mg/mL)

Note: HCL IS hydrochloride.

membranes used for osmotic drug delivery in 0-60% ethanol solutions (28). Although drug release from the analyzed osmotic-controlled release oral deilvery systems increased slightly, it was fully controlled, and no morphological changes to the dosage form occurred. The system maintained its functionality, and no potential for dose dumping was reported.

Roberts et al. studied the influence of alcohol on the release of aspirin from HPMC matrix tablets (29). They found that ethanol retarded hydration of the polymer and produced a more rapid initial drug dissolution but overall did not result in dose-dumping.

The influence of ethanol on the *in vitro* release of opioid drugs from various ER formulations (e.g., tablets, capsules, and suspensions) was examined by Walden et al. An extrapolation of the findings to the likely outcome *in vivo* indicated no risk of dose dumping (27).

Traynor et al. studied the potential for dose dumping in hydro-alcoholic media from three commercially available opioid analgesic (tramadol) formulations. The formulations provided 24-h dissolution using release-controlling coatings (30). The authors found that for two products (Ultram ER tablets and T-long capsules), the release of tramadol significantly increased in the presence of alcohol. Conversely, a decrease in the rate of drug release in hydro-alcoholic media was recorded for Tridural ER tablets.

Skalsky et al. analyzed the effect of alcoholic beverage concentrations up to 40% (v/v) on model highly water-soluble drugs, diltiazem hydrochloride (HCl) and metoprolol succinate, using both methacrylic copolymers and HPMC in matrix formulations (22). Drug-release behavior was unchanged in all media. However, the authors suggested a significant difficulty in correlating *in vitro* data to potential *in vivo* results due to the unpredictable effect of alcohol on absorption, metabolism, and excretion from the human body.

Levina et al. investigated the effect of hydro-alcoholic solutions on hydration, gel formation, and drug release from HPMC ER tablets and reported that hydro-alcoholic media containing up to 40% ethanol did not affect the performance of the matrices (18). Investigation of the effect of hydro-alcoholic solutions on textural and rheological properties of various controlled-release grades of hypromellose was also described by Missaghi et al. (31).

According to Ager et al., the effect of ethanol on pseudoephedrine HCl from HPMC ER matrix systems depended on the qualitative and quantitative composition of the tablets (32). The authors claimed that the drug release may be affected when using a filler with decreased solubility in ethanol (e.g., lactose or starch) and formulations containing fillers that have both poor aqueous and ethanol solubility (e.g., microcrystalline cellulose) might have no effect on drug release.

The influence of hydro-alcoholic media on PEO ER matrices has not yet been investigated. This research studies the influence of hydro-alcoholic media on the hydration and swelling properties of pure PEO compacts manufactured using different viscosity grade of Polyox, and drug release from ER matrices using two model drugs with different aqueous solubilities.

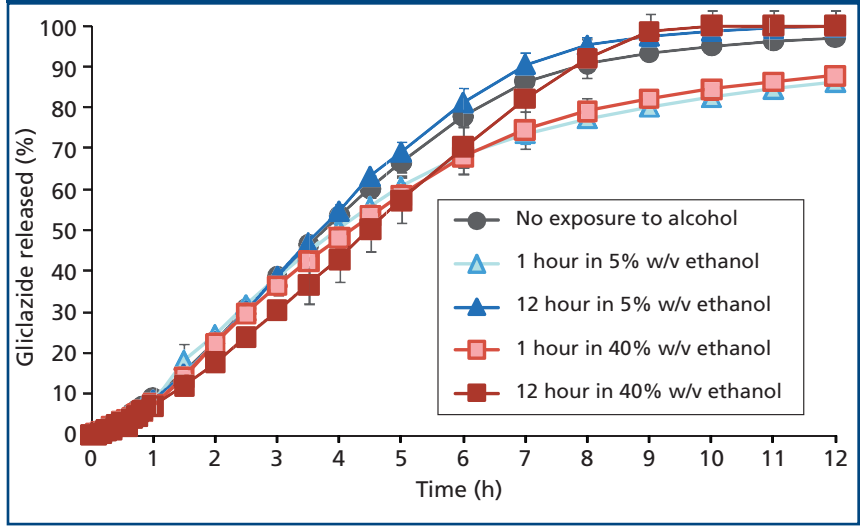
Materials and methods

Formulation and preparation of PEO ER matrices. The influence of hydro-alcoholic media on formulations of practically water insoluble gliclazide and freely water soluble metformin HCl was investigated. Two 12-h release PEO matrix formulations were developed containing gliclazide or metformin HCl, PEO (i.e., Polyox 1105 or 301) as a matrix former, microcrystalline cellulose (MCC) as a filler, fumed silica as a flow aid, and magnesium stearate as a lubricant (see Table II). Table III shows the solubility of the drugs, polymer, and filler in water and alcohol.

Both formulations, batch size 400 g, were blended in a shaker-mixer (Turbula, Bachofen). Microcrystalline cellulose and fumed silica were first screened through a 500 µm (35 mesh) sieve to homogenize the powder. The rest of the ingredients, except the lubricant, were added and blended for 10 min at 64 rpm. Magnesium stearate was then added and the formulations were mixed for an additional one minute.

Tablets were manufactured using an instrumented 10-station rotary tablet press (Piccola, Riva) operating at 20 rpm. Gliclazide tablets with a target weight of 200 mg were produced using 7 mm normal concave tooling at 20 kN (255 MPa). Metformin HCl matrices with a target weight of 1000 mg were manufactured using 7 × 18 mm concave caplet tooling at 20 kN (79 MPa).

Figure 1: Gliclazide 30 mg release profile from polyethylene oxide extended-release matrices in different media containing 0, 5 or 40% w/v ethanol ($n = 3$).



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Dissolution studies. Dissolution tests were conducted in a *USP* compliant dissolution bath (Sotax) using Apparatus II (i.e., paddles) with 8-mesh (2.38 mm) quadrangular baskets (QLA) in 1000 mL purified water, 5% or 40% w/v ethanol (USP/BP Hayman) solutions at 100 rpm and 37.0 ± 0.5 °C.

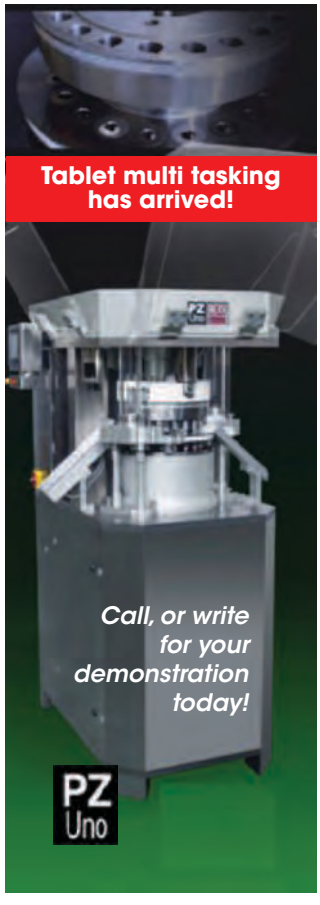

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Figure 2: Metformin HCl 500 mg release profile from PEO ER matrices in different media containing 0, 5 or 40% w/v ethanol ($n = 3$).

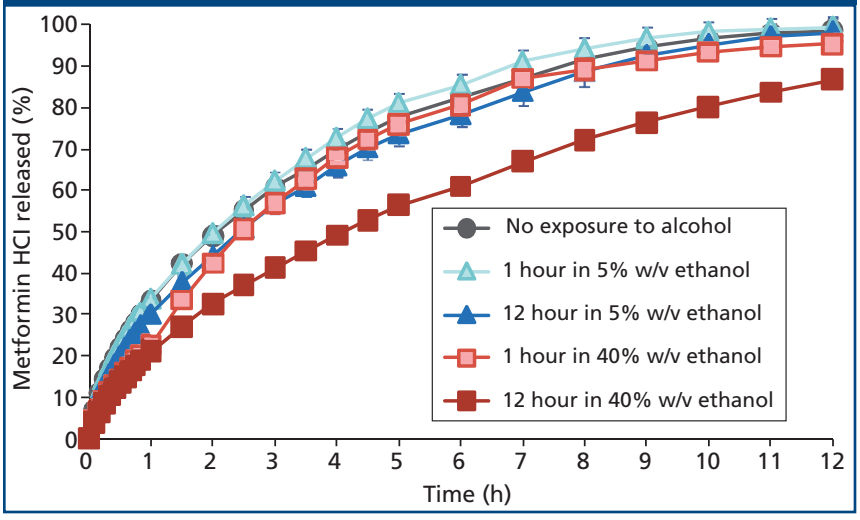

Table IV: f_2 values for drug release profiles from polyethylene oxide matrices in hydro-alcoholic media compared with non-exposure to ethanol solutions.

Duration of exposure to alcohol containing media (h)	5% w/v ethanol		40% w/v ethanol	
	1	12	1	12
Gliclazide formulation	62	91	74	59
Metformin HCl formulation	96	75	58	42

Table V: Values of the kinetic constant (k), diffusion exponent (n) derived from Equation 1, and correlation coefficients (R^2) for PEO ER matrices in various media.

	Dissolution testing conditions	k	n	R^2
Gliclazide formulation	No exposure to alcohol	9.095	1.2932	0.9991
	1 h in 5% v/v ethanol	8.743	1.3177	0.9888
	1 h in 40% v/v ethanol	7.676	1.3691	0.9945
Metformin HCl formulation	No exposure to alcohol	32.964	0.6084	0.9988
	1 h in 5% v/v ethanol	33.498	0.6284	0.9964
	1 h in 40% v/v ethanol	24.240	0.7431	0.9939

Tablets were subjected to the hydro-alcoholic media for duration of 12 h, or 1 h followed by 11-h dissolution in water.

Absorbance was measured with a dual-beam UV–vis spectrophotometer (PerkinElmer) using 5 mm quartz cells at a wavelength of 228 nm and 0.1 mm cells at 233 nm for gliclazide and metformin HCl, respectively. Tablets were analyzed in triplicates using an automated sampling device, and mean with standard deviation values were reported.

The drug release profiles in hydro-alcoholic media were compared to those in purified water using the f_2 factor. An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar (7, 38).

To investigate the mechanism of drug release in various media, the release data between 5 and 60% were fitted to the following equation (16, 39–40):

$$Q = kt^n \quad \text{(Eq. 1)}$$

where Q is the percentage drug released at time t, k is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent that indicates the drug release mechanism (39–40).

For matrix tablets, an n value close to 0.5 indicates predominantly diffusion control of drug release. An n value around 1.0 indicates erosion or relaxation control mechanism of drug release (41–42). Intermediate values suggest that both diffusion and erosion contribute to the overall release mechanism (18).

The values of n and k are inversely related, such that a decrease in n value results in a k value increase. A high k value may suggest a burst drug release from the matrix (43–44).

Preparation and testing of PEO compacts. Three viscosity grades of PEO were tested (i.e., Polyox 1105, 301, and Coagulant). PEO compacts with a target weight of 300 mg were manufactured using hydraulic automatic press (Auto T8, Atlas, Specac) and 10 mm flat-faced tooling at a compression force of 20 kN (255 MPa).

Compacts were tested in a *USP*-compliant AT7 Sotax dissolution bath using Apparatus II (i.e., paddles) with large (15 × 31 mm) sinkers (Sotax), in 900 mL of 0:100, 25:75 and 50:50 w/v ethanol:purified water mixtures at 100 rpm and 37 ± 0.5 °C.

The swelling properties of the compacts in various media were determined using a modified version of the method described by Tahara et al. and Kavanagh and Corrigan by measuring the wet weight of the hydrated PEO compacts at 15, 30, 60 and 120 mins (45, 46). Each compact was placed into a preweighed plastic container; the excess media was drained and blotted from around the tablet without touching it. The compact and the container were weighed, and the wet weight of each tablet was established. Every determination at each time point was performed in triplicate, and average and standard deviation values were calculated.

The ratio of the wet weight (W_w) to the initial weight (W_i)

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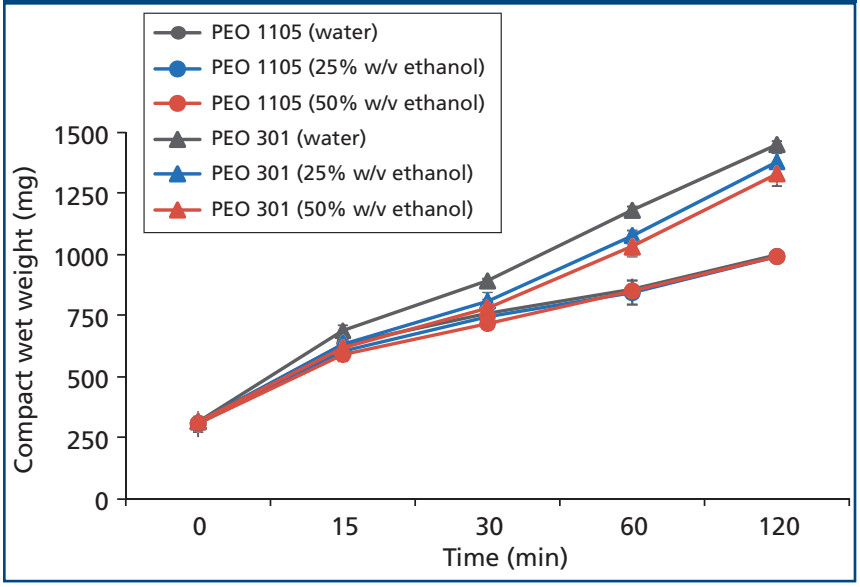
Figure 3: Effect of hydro-alcoholic media containing 0, 25 or 50% w/v ethanol on wet weight of PEO (Polyox 1105, 301 and Coagulant) compacts ($n = 3$).



of the compacts was calculated, as an indication of the extent of matrix relative swelling, similar to the Panomsuk et al. approach, as described in the following equation (47):

$$\text{Relative compact swelling} = W_w \div W_i \quad \text{(Eq. 2)}$$

Results and discussion

The effect of hydro-alcoholic media on drug release from PEO ER matrices. Robust PEO ER matrices with strength values of 2.32 MPa (13.0 ± 0.2 kp) for gliclazide and 0.70 MPa (14.0 ± 0.5 kp) for metformin HCl were produced. Reproducible drug release profiles were obtained for both formulations in all tested media. No dose dumping from the PEO matrices was observed even after 12-h exposure to the hydro-alcoholic media.

Figure 1 and Table IV show that gliclazide release was not significantly affected by either 1- or 12-h exposure to 5% or 40% w/v ethanol solutions. The differences observed in the dissolution profiles can be attributed to the different solubility of the drug in ethanol (see Table III).

Metformin HCl release from PEO ER matrices in hydro-alcoholic media was similar to the dissolution results in water in all the tests ($f_2 > 50$), with the exception of the 12-h exposure to 40% w/v ethanol ($f_2 = 42$), where drug release was significantly slower (see Figure 2 and Table IV). This result can be explained by a reduction in metformin HCl solubility from 450 mg/mL in water to 295 mg/mL in 40% v/v ethanol (18). However, such extreme conditions (i.e., high concentration of ethanol during a prolonged period of time) are unlikely for *in vivo* conditions. In the human body, tablets taken with alcohol are unlikely to be exposed to a 40% v/v hydro-alcoholic medium for a 12-h period because of the rapid absorption of ethanol from the gastro-intestinal tract (18, 33). This study did not reveal any effect on dissolution after 1-h exposure of PEO ER tablets to hydro-alcoholic media for either active.

Drug-release variability, in particular with gliclazide, increased when matrices were tested in alcohol. The standard deviation for gliclazide tablets subjected to hydro-alcoholic media increased from 2.3% (no exposure to alcohol) up to 3.6% (exposure to 5% w/v alcohol) and up to 5.6% (exposure to 40% w/v alcohol), respectively (see Figure 1). This result may be due to the influence of ethanol on hydration of the polymer and erosion of the gel structure on the surface of the matrix.

The values of the kinetic constant (k), the release exponent (n), and correlation coefficient (R^2) determined from the drug release data are presented in Table V. As gliclazide is practically insoluble in water and slightly soluble in alcohol (see Table III), its release from ER hydrophilic matrices was expected to occur predominantly by gel erosion. This was confirmed by high n values (1.3–1.4) suggesting that erosion was the main mechanism of gliclazide release from PEO matrices in all studied dissolution media.

On the other hand, a combination of diffusion and erosion ($n = 0.6$-0.7) was observed with metformin HCl (see Table V), which was anticipated due to its high aqueous drug solubility. Metformin HCl solubility changes from freely soluble in water to slightly soluble in alcohol (see Table III), resulting in a greater erosion contribution to the drug release from the tested PEO matrices. This was reflected by an increase in n value from 0.61 in water to 0.63 and to 0.74 in 5 and 40% w/v ethanol solutions, respectively. These findings agree with the Roberts data showing that ethanol affects the kinetics and mechanism of drug release from hydrophilic matrix tablets, but does not result in dose dumping (29).

Because the values of n and k are inversely related, k values changed slightly from 32.96 in water to 33.50 and 24.24 for metformin HCl tablets exposed to 5% and 40% w/v ethanol solutions, respectively. These results imply that the rate of drug release is slightly slower in 40% w/v ethanol solution than in water.

For both formulations, greater erosion contribution to the drug release from the tested matrices was observed in ethanol solutions compared with aqueous media. The results of this study identified similar trends to the previously

Table VI: Effect of hydro-alcoholic media on wet weight of Polyox compacts ($n = 3$).

Time (min)	Weight (mg) Polyox 1105			Weight (mg) Polyox 301			Weight (mg) Polyox Coagulant		
	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol
0	307±11	309±6	308±81	315±1	315±10	314±4	317±5	308±2	316±4
15_5	635±56	601±6	589±31	688±25	634±34	616±45	714±19	630±18	620±17
30	760±49	744±9	718±26	893±13	807±40	778±39	942±18	823±34	797±17
60	858±40	846±23	847±22	1183±20	1075±28	1031±38	1217±5	1056±21	1022±17
120	996±44	989±49	994±25	1453±15	1376±44	1331±49	1548±36	1383±34	1337±17

Table VII: Effect of various media on relative swelling of Polyox compacts ($n = 3$).

Time (min)	Relative swelling Polyox 1105			Relative swelling Polyox 301			Relative swelling Polyox Coagulant		
	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol
15	2.07	1.94	1.91	2.19	2.01	1.96	2.25	2.05	1.96
30	2.47	2.41	2.33	2.84	2.56	2.48	2.97	2.67	2.53
60	2.79	2.74	2.75	3.76	3.41	3.28	3.84	3.43	3.24
120	3.24	3.20	3.23	4.62	4.36	4.24	4.89	4.49	4.24

published data for HPMC ER matrix systems (18). This finding is interesting in light of gastrointestinal tract motility. According to Bode and Bode, alcohol may interfere with the activity of the muscles surrounding the stomach and the small intestine and thus alter the transit time of food through these organs (48–49). In humans, alcohol's effect on gastric motility depends on the alcohol concentration and accompanying meals. In general, beverages with alcohol concentrations above 15% appear to inhibit gastric motility and thus delay the emptying of the stomach. In the small intestine, alcohol decreases the muscle movements that help retain the food for further digestion (i.e., the impeding wave motility). However, alcohol does not affect the movements that propel food through the intestine (i.e., the propulsive wave motility) in either alcoholics or healthy subjects.

It is also important to take into account the solubility of additional excipients (e.g., fillers, bulking agents, and surfactants) used in the formulation. The most popular fillers used in hydrophilic matrix systems can be ranked in ascending order according to their solubility in ethanol: MCC and dicalcium phosphate dehydrate, pregelatinized starch, and lactose (18). Practically insoluble in both water and aqueous alcoholic solutions, MCC was the filler least likely to be affected by the dissolution media choice in this study.

The effect of hydro-alcoholic media on swelling of pure PEO compacts. Mechanically strong compacts (i.e., >21 ±0.5 kp, > 3.3 MPa) were produced for all three grades of PEO tested in this study. In water and hydro-alcoholic solutions all PEO tablets underwent swelling and gelation without any disruption to the matrix integrity. A similar progressive weight gain by compacts made of various viscosity grades of PEO was observed in water and hydro-alcoholic media (see Figure 3 and Table VI). For high viscosity grades of PEO (e.g., Polyox 301 and Coagulant), a slightly lower swelling and gel formation in the presence of ethanol was recorded. This result can be attributed to a decrease in polymer solubility in alcohol compared with water (see Table III), retarded hydration of the polymer, and the resulting change in gel viscosity (29, 31, 50–51).

Table VII shows that the extent of swelling increased with increasing molecular weight (MW) of PEO from 900,000 Da (Polyox 1105) to 4,000,000 Da (Polyox 301). However, no significant difference in compact relative swelling was observed when MW was further increased from 4,000,000 Da (Polyox 301) to 5,000,000 Da (Polyox Coagulant).

Conclusion

Extended-release PEO tablets of the practically water insoluble drug gliclazide (30 mg) and freely soluble metformin HCl (500 mg) retained their hydrated structural integrity when exposed to 5% and 40% w/v ethanol solutions for up to 12 h. The matrices did not fail in hydro-alcoholic media. Small differences in drug release profiles were explained in terms of drug solubility in various media. The results of this study identified trends similar to those in previously published data for HPMC ER matrix systems.

Exposure of compacts of three different viscosity grades of PEO (Polyox 1105, 301, and Coagulant) to water or hydro-alcoholic solutions had shown gradual swelling and gelation without any disruption to the tablet integrity. The

compact wet weight appeared to be only slightly lower in hydro-alcoholic solutions compared to water. The extent of their relative swelling was found to increase with increasing molecular weight of PEO from 900,000 Da to 5,000,000 Da. No significant difference in compact relative swelling was observed when MW increased further from 4,000,000 Da (Polyox 301) to 5,000,000 Da (Polyox Coagulant).

This study clearly indicates that PEO matrices produces consistent drug release in water and in hydro-alcoholic media with no signs of a potential dose dumping.

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Multiunit Particulate Systems

A Current Drug-Delivery Technology

Mitesh D. Phale and Abhijit V. Gothoskar

Multiunit particulate systems (MUPS) have received a great deal of consideration in recent years as a controlled drug-delivery method. The current review describes the role and selection of excipients, pellet core, coating materials, and compression with various cushioning agents. MUPS technology enables firms to achieve the desired and therapeutic release with minimal side effects. Thus, MUPS can open a new area of research for scientists with many opportunities for the formulation of controlled- and delayed-release oral dosage forms.

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Oral drug-delivery systems are the most acceptable form of controlled-release system to patients. Scientists have shown growing interest in modified-release oral dosage forms in recent years. Current technologies, such as oral multiparticulate drug-delivery systems (MDDS), have gained immensely in importance, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate.

These systems release the drug with constant or variable release rates, thus maintaining drug concentration within the therapeutic window for a prolonged period of time. The desired release profile facilitates controlled absorption through the target site in the body, ensures good therapeutic activity, and reduces side effects (1). MDDS comprises a large number of small discrete particles (i.e., active ingredient and excipients), each demonstrating desirable features. They are prepared by methods including extrusion–spheronization, pelletization, granulation, spray drying, and spray congealing.

Multiunit particulate systems

Multiunit particulate systems (MUPS) are a novel MDDS technique for controlled and modified drug delivery. MUPS offer various advantages over other systems, including reduced risk of local irritation and toxicity, predictable bioavailability, reduced likelihood of dose dumping, minimized fluctuations in plasma concentration of drug, and high dose-strength administration (1). Multiparticulate systems show more reproducible pharmacokinetic behavior and lower intra- and intersubject variability than conventional (i.e., monolithic) formulations (2). Tableting of pellets reduces the esophageal residence time, compared with capsules, and improves physicochemical stability, compared with suspensions (2, 3).

The applications for which MUPS formulations are developed include taste masking (i.e., orodispersible MUPS tablets), enteric-release (e.g., of acid-labile drugs), and modified- or controlled-release orodispersible drugs for geriatric or pediatric patients. The technology of prepar-

ing compacted MUPS ensures that the desired objectives (e.g., taste masking coupled with orodispersibility as well as modified-release characteristics) are effectively achieved.

A good example of a MUPS is AstraZeneca's Losec, an antiulcer drug, the second-highest-selling pharmaceutical product in Sweden in 2002 (3). The product consists of microencapsulated drug granules tableted with excipients (4). Other marketed MUPS formulations include Galanil PR (Galantamine HBr) for Alzheimer's disease, antiobesity drug Lipidown (Orilistat), and Esomezol (Esomeprazole Sr) for erosive reflux esophagitis, which are all manufactured by Hanmi Pharmaceutical.

Figure 1: Pelletization process.

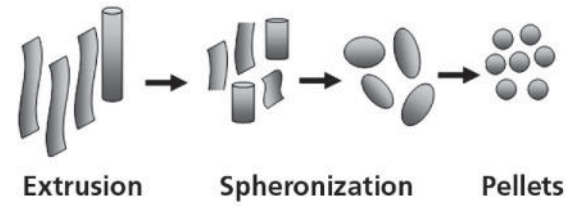


Figure 2: Pelletized tablet with drug embedded polymer matrix system.

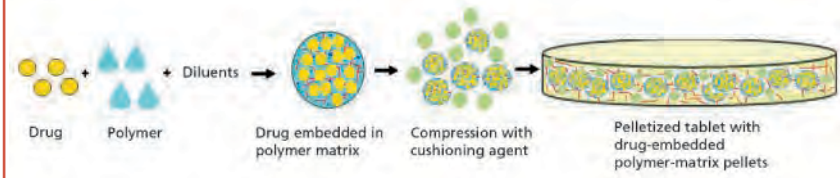
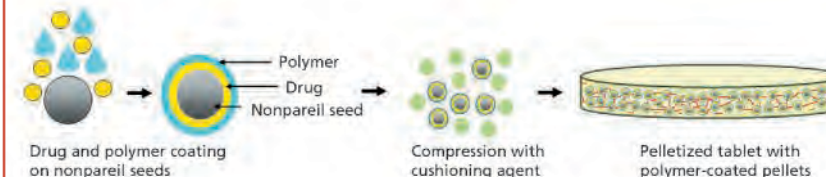


Figure 3: Pelletized tablet with polymer coated pellets.



Challenges in the formulation of multiunit particulate systems

Each discrete particle in a MUPS product incorporates its own release characteristics and further contributes to the product's therapeutic activity. Compressing these subunits without affecting their individual release profiles is a major challenge of MUPS technology because compacting subunits may lead to structural changes in the coating and consequently alter drug-release behavior (5).

Other challenges for manufacturing pellets in tablets (i.e., MUPS) are weight variation, poor hardness, and friability. To prevent subunits from being altered, formulators include a cushioning agent (i.e., an excipient with protective properties) in the tablet formulation.

The compression-induced changes in the structure of the subunits may depend on numerous formulation factors, such as the type and amount of coating, the properties and structure of the substrate pellets, and the incorporation of excipient particles. During MUPS formulation, scientists must consider process variables such as the nature of the polymer; the shape, porosity, and density of pellets; compression force and content of coated pellets in the tableting blend; the wall thickness of coating; and the nature of the excipients.

Pelletization and multiunit particulate systems

Pellets are manufactured by both wet and dry granulation techniques or by layering. Extrusion–spheronization is a wet-granulation technique that helps in the preparation of pellets or spherical agglomerates. The process involves a blending stage, in which active ingredients are blended with excipients and mixed with suitable binding solutions to form a heavy plastic mass. This mass is subjected to extrusion to form extrudates of equal length. After extrusion, the materials undergo a spheronizing stage that rounds extrudates by cutting them and rolling them into spheres (see Figure 1).

Manufacturers create modified-release systems in two main ways. They either coat spherical, uncoated pellets or embed a drug in a polymer matrix system (6). The uncoated drug–polymer pellets prepared by extrusion–spheronization are subjected to compression into tablets (see Figure 2). In another technique, the polymer or release-controlling material is coated along with the drug onto the uncoated pellet to form a nonpareil seed (see Figure 3). These drug–polymer coated pellets are compressed into tablets to obtain MUPS.

Compressibility and compactibility

The ability of a powder to decrease in volume under pressure is called compressibility, and the ability of the powdered material to be compressed into a tablet of specific strength is called compactability (7). According to one theory, the compaction sequence for elastic materials includes particle rearrangement, plastic deformation, and elastic deformation (8). In Van der Zwan and Siskens's theory of the compaction of pellets, the process of volume reduction involves the filling of interparticle voids, where the secondary particles undergo readjustment; the fragmentation and plastic deformation of secondary particles; the filling of intraparticular voids, where primary particles rearrange, making the mass more dense; and the fragmentation and plastic deformation of the primary particles (9).

ALL FIGURES ARE COURTESY OF THE AUTHORS

In an entirely different theory of compaction and volume reduction, Johansson stated that the secondary particles rearrange to fill interparticle voids where the strength of the compressed powder is too low due to low bonding force. Next, the surfaces of the secondary particles are flattened with local deformation. Then, as secondary particles undergo bulk deformation, they simultaneously become densely packed, and bonding strength increases significantly. Finally, low inter- and intragranular porosity causes the compression process to stop with less volume reduction of the bed but with higher bonding within the particles (10).

The major challenge of a formulator is to retain pellet-properties after the compaction process. To aid formulators, this article will describe the factors involved in the compaction and consolidation of coated and uncoated pellets.

Compression of coated pellets

Preparing compacted MUPS (i.e., compressing coated pellets to achieve multiple objectives) is a challenging task. During compaction, the polymeric coating may not withstand the compression force, thus affecting the surface of polymer and the pellets, which could cause the drug to be released in an undesired manner.

Hence, thorough process optimization is needed for the compaction of coated pellets. The main variables involved are the compression force and the velocity of the punches. The hardness, thickness, and porosity of the tablets must be maintained. Other important factors concerning the preparation of multiunit tablets are the properties of the barrier coating and the inclusion of protective excipient particles in the tablet formulation, and these parameters have been investigated extensively.

Pellet core. Many formulators have successfully studied and investigated the compression behavior of pellets consisting of various excipients. The selection and study of the material used to manufacture pellets is important to achieve the desired release pattern (11). The comparison between soft and hard pellets revealed that the pellets with soft constituents had the greater chance that intergranular pore spaces would be filled because the primary particles can move within the agglomerate. Harder pellets tend to fail at the surface because of the pressure of compaction.

Nicklasson studied the behavior of microcrystalline cellulose (MCC), alone and in combination with polyethylene glycol and dicalcium phosphate pellets, during and after compression. He concluded that pellets are deformed after compression, depending on their capacity for, mode of, and resistance to deformation. Nicklasson also studied polyethylene glycol as a cushioning agent to analyze the compression behavior of pellets. For the study, he used MCC-based beads loaded with theophylline, which are hard, and softer beads prepared with glyceryl monostearate (12).

Wang attempted to study the compression of lactose and MCC in various concentrations of powder and pellets. MCC-based pellets lost their plasticity during granulation and hence showed poor compactability, compared with lactose-based pellets (13). Iloanusi and Schwartz studied the crucial role that plastic deformation plays in compression by adding wax to the MCC bead formulations. Pellets with wax as a cushioning agent had more compressibility than beads without wax as a compression modifier (14).

Salako confirmed the advantages of softening materials during compression. On application of initial compaction pressure, the soft beads ruptured. On further application of pressure, the beads deformed and formed a network. Because of the soft nature of the beads, the material readily underwent deformation and rearrangement. Harder pellets are compact, and upon the application of compaction pressure, they underwent reduction in volume by particle rearrangement, not because of bond formation, compared with soft pellets (15).

Salako conducted a similar study of pellets' deformability and tensile strength using MCC-based beads loaded with theophylline, which are hard. Soft pellets were prepared with glyceryl monostearate (15).

Pellets undergo structural modifications during compaction. They need elasticity and flexibility to withstand compaction pressure. The ideal pellets are strong, not brittle, and have a low elastic resilience. They should deform under load application and load recovery without fracture (16). Knowledge of the compression behavior of uncoated pellets can provide a basis for the manufacture of multiunit tablets from barrier-coated pellets without damaging their coating.

Size and shape. Pellets undergo deformation after compression. Hence, the size of the pellets affects their compaction properties and the drug release from compacted pellets. Large pellets tend to undergo deformation more readily than small ones. Small pellets are stronger than large ones; they withstand compression pressure with less deformation (17). The strength of the pellets affects the final strength of the compressed tablet and helps ensure the desired release rate.

Johansson proposed that the deformation of individual pellets could be correlated with their size. A higher degree of deformation was observed with large pellets than with small pellets. As the size of pellets increased, the number of force-transmission decreased, which increased the contact force on each pellet (18). Isometric-shaped pellets offered fewer contact points and more uniform drug release than anisometric-shaped particles.

In addition to size, the shape of pellets affects the compression behavior and tablet-forming ability of granular materials. Irregular shapes induce complex compression behavior in granules. They increase the attrition of the granules, thus resulting in increased deformation (19–20). Flament found that, after the application of similar quantities of coating on pellets, small pellets were more fragile than large pellets. The probable reason is that small pellets'

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Metabolic Syndrome

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Metabolic syndrome is not a single disease, and monitoring patient outcomes to a therapeutic regimen must take into account a complex cluster of factors and biomarkers. This webinar reviews the medical indications defining the syndrome and presents case studies in clinical trial design that demonstrate how to effectively monitor relevant factors and biomarkers in order to gauge with accuracy in patient outcomes.

PRESENTERS:

Lionel Hovsepian, MD
Clin Pharm, Clinical Unit Director, SGS Life Science Services, France

Ishwarlal Jialal, MD, PhD
Robert E. Stowell Endowed Chair in Experimental Pathology, Director of the Laboratory for Atherosclerosis and Metabolic Research, and Professor of Internal Medicine at the University of California (Davis), and editor-in-chief of the *Journal of Metabolic Syndrome and Related Disorders*

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Biopharmaceutical Characterization

This webinar will provide a detailed look into FDA's PIlot Program for QbD-based submissions of complex biotechnology products as well as industry best practices in bioprocessing. New analytical techniques and tools for conditions within a bioreactor as well as the integrity and uniformity of the drug product will also be discussed.

PRESENTERS:

Anurag S. Rathore, PhD
Consultant, Biotech CMC Issues, Faculty Member, Department of Chemical Engineering Indian Institute of Technology, New Delhi, India

Richard Easton, PhD
Team Leader, Carbohydrate Analysis, SGS M-Scan, UK

Ron Snee
President, Snee Associates, LLC

Quality Control

Preventing Cross-Contamination in a Pharmaceutical Manufacturing Environment

This webinar will discuss best practices for environmental monitoring and cleaning validation to prevent cross-contamination on the laboratory and manufacturing floor. Facility management, pharmaceutical water, and microbials will be discussed. Presentations will be in the context of ISPE's Risk-MaPP guideline.

PRESENTERS:

Kimberly K. Ray
LSS Black Belt, Secretary of the ISPE containment steering committee, and Sr. Manager Project Management/Customer Service, OSO Biopharmaceuticals

Richard Forsyth
Senior Consultant with Hyde Engineering & Consulting

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

For questions contact Jamie Carpenter at jcarpenter@advanstar.com

increased surface area reduced the film-coating thickness (21). Furthermore, increases in particle size resulted in more damage to the coating, as indicated by larger differences between the release profiles of tablets and uncompressed pellets (20).

Beckert compacted coated pellets of two crushing strengths with different excipients and concluded that the harder pellets were better able to withstand compression forces because they deformed to a lesser degree and their film coatings were less susceptible to rupture (22). Ragnarsson found that the compaction of small pellets had less effect on drug release than the compaction of large pellets. He also concluded, however, that the effect of pellet size depended on the choice of coating material, as well as on the amount and properties of the pellets and the excipients forming the tablet (23).

Density and porosity. Pellet density and size play an important role in achieving content and weight uniformity. Because of their intragranular porosity, pellets tend to densify. By modifying their intragranular porosity, manufacturers can deform and densify pellets during compression (24–27). Pellets with a narrow size distribution and excipients of similar sizes, shapes, and densities can prevent segregation (28). The critical density for achieving prolonged gastric residence may be between 2.4 and 2.8 g/cm^3 (29). The amount and choice of material used for binding or granulating the powders during pelletization, and the compaction pressure, have a direct effect on the porosity.

Unlubricated pellets also require higher pressures than lubricated pellets (5). A study by Bodmeier revealed that an increased proportion of water as granulating fluid in the mixture led to hard and less porous tablets with a slow drug-release pattern. Similarly, pellets prepared using 95% ethanol as a granulating fluid showed good compressibility in contrast with pellets prepared with water (5). Using 95% ethanol during granulation formed strong intergranular bonds with an increased porosity, which finally increased the deformation of the formed pellets during compaction into tablets.

Porosity also can affect drug release. Tuton showed that pellets of high porosity were densely packed and deformed, and that the drug release from these pellets was not affected. But upon compaction of pellets with low porosity, the pellets were compressed with slight densification and deformation, leading to increased drug release. Using highly porous pellets did not alter the drug release after compression, in comparison with pellets with low porosity (30).

Compression force. Compression force is a critical parameter that must be optimized during tableting of pellets. Several studies investigated the compression force required for compressing pellets and found that 15 KN was sufficient for tablets with smooth surfaces. Flament studied the compression of theophylline-loaded pellets with acrylic polymer. Upon the application of compression pressure, the pellets were compacted by deformation at 6 KN. Further investigation revealed that increasing the compaction force to 20 KN did not alter the dissolution rate significantly (21).

Protective particles. Protective particles, also known as cushioning agents, help prevent damage to the drug–polymer-loaded core pellets. Protective particles rearrange themselves between the pellets and reduce the void space to prevent direct contact of pellets after the application of compression pressure. Preferred excipients are agglomerates (e.g., pellets or granules) that lower the risk that pellets will separate by size or density during processing, thus leading to weight variation or dose nonuniformity. When used as cushioning agents, primary particles (e.g., powder) give rise to the above problems (16, 21, 31). The cushioning effect of an excipient depends on its particle size, volume, and compaction properties. The method by which the particles undergo volume reduction needs to be studied. Several studies proved MCC and polyethylene glycol to be good excipients for compaction because of their plastic deformation (22, 32–34). Studies also proved that lactose, which undergoes fragmentation upon compression, offers better protection than MCC (35).

However, studies of 14 excipients proved that excipients that show good plastic deformation during compression give the best protection to the coating material (36). Particle size is an important factor in preformulation, and some studies suggested that particles smaller than 20 μm prevent damage to the coating. Increased dissolution rate was observed with particles bigger than 20 μm (29, 37). Using wax as a cushioning agent during pellet compression also is of great help to the formulator because it prevents damage to the coating during compression (38).

Nature of polymer. Polymers play an important part in any controlled- or modified-release dosage form. The final release of the drug from the formulation depends on the polymer used. A polymer must have appropriate plastic and elastic properties to withstand the shear of compression and compaction. Various polymers currently used to modify the release of pellets are either cellulosic polymers (e.g., ethyl cellulose) or acrylic polymers (e.g., Divakar's Polex, Evonik's Eudragit, or BASF's Kollicoat). The most frequently used polymers to extend the release of water-insoluble drugs are ethyl cellulose and ammonio methacrylate copolymers (39). Film-forming polymers have satisfactory elastic properties that prevent the rupture of the coating polymer, and good plastic properties that prevent deformation during compression.

Studies revealed that not only does the coating material affect compression properties, but also the solution in which polymer is dispersed or dissolved. The process entails dispersing polymer in water as pseudolatex or dissolving the polymer in an organic solvent. Investigations were conducted on ethyl cellulose to study its sustained-release properties after coating and compression in tablets. Ethyl cellulose improved pellets' puncture strength and elongation by making them brittle. The mechanical properties of

ethyl cellulose were less affected after it was plasticized with pseudolatexes (19). Beads composed of alternating layers of ethyl cellulose, drug, and cushioning agent are less brittle than those that include only drug and ethyl cellulose.

Chang and Rudnic found that the solvent-based coatings were affected less by compression than the aqueous-based coatings were. Solvent-based coatings improved flexibility and mechanical stability in comparison with aqueous-based coatings (40). The coated pellets ruptured on compression, which affects the film formed on the pellets' surface.

To minimize or overcome rupture during compression, Bodmeier suggested placing the compressed pellets in a hot-air oven above their glass-transition temperature (5). The brittle and elastic properties of MCC pellets were modified by applying a water-based ethyl cellulose coating to them. Thus, plastoelastic properties were introduced to the pellets after coating, which improved their deformation characteristics (31).

Bechard and Celik showed that aqueous dispersions of ethyl cellulose for compression into multiunit tablets can, however, lead to coating failure through the formation of cracks and flaws (31–32). Films formed with high elasticity and apparent Newtonian viscosity delivered the maximum protection to the pellet core and coating on compaction (16). Lehmann suggested that the coating should be elongated at least 75% at the break to prevent the coating from rupturing during compression (41).

Thickness of polymer coating. The amount of coating affects how much compaction can modify it. Applying a thick polymeric coating to the surface of pellets imparts good elasticity and crushing strength to them (22). Damage to the coated pellets thus can be minimized during compression by applying a thick, rather than thin, coating of polymer solution (21–22). Bodmeier observed increased elastic and plastic deformation upon application of thick coating (5). The thickness of applied coatings provides good resistance to frictional forces, thus showing a direct dependence of cracks and elasticity on the film. To prevent the coatings from rupturing during compaction, the coating should have good elasticity and flexibility and be able to undergo structural changes and adapt to the deformation process (16, 22, 40, 41).

Plasticizer. Plasticizers are added to polymeric dispersions, especially to water-dispersions, to lower their glass-transition temperature and expedite the coalescence of the distinct polymer particles in the dispersion. Thus, coalescence of polymer particles directly relies on the time and temperature of coating and postcoating processes. Onions proposed a two-stage theory for the process of coalescence of aqueous polymeric dispersions.

The first stage includes the evaporation of the aqueous layer and the formation of a dry, transparent, apparently continuous film on the surface of the coated material. The coalescence of distinct polymer particles is completed gradually in the second stage. The water in the interstitial spaces starts evaporating slowly, bringing the separate particles close to each other and finally fusing the particles to form a strong and continuous film on the surface of the coated material (42–43). Further studies revealed that the amount of plasticizer did not influence drug release from compacted reservoir pellets (44). The flexibility of the aqueous-based coatings was improved by adding plasticizers, but Aulton observed that plasticizers led to a reduction in tensile strength (45). Felton proposed that increasing plasticizer content would increase the tensile strength of film-coated beads. The increased degree of plasticization of the polymer made the film more elastic and allowed it to withstand the deformation process during compression (46).

Conclusion

With its promising controlled-release mechanism for oral delivery, MUPS will be a focus of future research and development. The selection of excipients plays a key role in the success of MUPS. A thorough understanding of the factors that affect the performance of MUPS helps the formulator tailor the drug-release profiles. MUPS may soon become one of the most popular oral controlled-release systems.

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FDA Introduces Spectral Libraries

Lucinda F. Buhse and Philip H. Merrell

In an effort to prevent contaminated, mislabeled, or counterfeit drug products from entering the US marketplace, FDA's Division of Pharmaceutical Analysis is building a spectral library of excipients that can be used to detect improper ingredients within a drug product on site. In collaboration with the International Pharmaceutical Excipients Council, the agency is asking for industry help in this effort. The authors describe the spectral-library project and address common questions.

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Globalization of the pharmaceutical supply chain has increased the challenges to FDA to ensure that drug products and ingredients are not contaminated, counterfeited, or mislabeled (1, 2). To help in this effort, the agency has developed rapid screening methods for pharmaceutical products and ingredients that can be deployed on portable instruments by field laboratories and inspectors for the screening of dietary supplements, pharmaceutical ingredients, and finished products on site (e.g., at border crossings, import centers, foreign manufacturing sites). Examples include detection of toxic and catalytic metals by X-ray fluorescence, detection of weight-loss drugs in dietary supplements by ion mobility spectroscopy, detection of diethylene glycol and ethylene glycol in glycerin, sorbitol or propylene glycol by Raman or near-infrared (NIR) spectroscopy (3–7). The deployment of such instruments will allow FDA inspectors to screen a large number of ingredients and products at the site of importation, in domestic commerce, or even at foreign drug manufacturing sites, and to determine which are suspect and should be detained, sampled, and sent to laboratories for confirmatory testing by traditional methods such as US Pharmacopeial testing. FDA is concerned about diversion into the legitimate supply chain of excipients that are unsuitable for use, as well as the possibility of tampering with an excipient during transit.

During the past year, FDA's Division of Pharmaceutical Analysis (DPA) has developed a deeper understanding of the value and limitations of library-based Raman and NIR spectral-correlation methods for rapid spectroscopic screening of pharmaceutical ingredients (8–10). The division has developed procedures for transferring spectral libraries across instruments from different vendors and platforms (e.g., laboratory, portable, and handheld).

DPA would now like to build an excipient library to be deployed on NIR and Raman portable instruments and used at points of entry or storage. To ensure a robust library, DPA is partnering with the International Pharmaceutical Excipients Council (IPEC) to reach out to manufacturers and distributors of common excipients to provide authentic samples to the agency to help build these libraries. This article provides details on how to participate, and some anticipated questions and answers.

Benefits of participation

Development and deployment of an excipient library to monitor for possible contamination, adulteration, tampering, and diversion into the qualified pharmaceutical supply

chain will improve safety of the drug supply, and thus, patient safety. Additional benefits include the following:

- An inspector can make an immediate determination as to whether laboratory analysis is necessary by performing a screening test. This approach would reduce delays associated with sending samples to a laboratory.
- Knowledge that FDA is screening excipients and that excipients are receiving a higher level of scrutiny should provide deterrence and add a layer of difficulty for anyone trying to infiltrate the supply chain.
- All parties can have an increased level of confidence that the material being identified is indeed from the qualified supplier.
- Materials that are different from the spectral reference standards can be flagged for additional investigation and, if warranted, subsequently added to the library.
- All parties will have increased assurance that goods were not tampered with, substituted, or otherwise falsified with regard to their origin during distribution.
- Screening and surveillance activities can enable rapid response to concerns of contamination, adulteration, and/or substitution in the supply chain reported to or identified by FDA.

Creation of this library will provide added assurance that a given excipient is of the expected quality. Consumers will have increased confidence in the quality of drug products based on this increased surveillance of the excipient supply chain.

Details of participation

Materials (i.e, excipient samples) would be shared with DPA in St. Louis using a Material Transfer Agreement (MTA). This agreement would allow DPA to accept material from vendors and distributors and protect intellectual property. A copy of the MTA and contact information can be obtained on the FDA's Office of Testing and Research website under Hot Topics, at www.fda.gov/AboutFDA/CentersOffices/CDER/ucm136930.htm.

Manufacturers are asked to provide multiple lots (at least three) of approximately 2 g each of excipients with a Certificate of Analysis for the lot. In the case where manufacturers do not supply directly to the US pharmaceutical industry, distributors may submit the excipient samples. Material should be representative of the potential spectral variability that might be expected in their product. Variables that might affect spectral variability would include the following:

- Manufacturing site
- Grade of material
- Expiration period
- Processing differences, including raw materials, operating conditions, and production equipment
- Time of year of harvest.

Samples should be accompanied by the following information where applicable:

- Name of manufacturer
- Manufacture site
- Excipient name
- Trade name
- Compendial or excipient grade
- Lot designation
- Date of manufacture
- Special handling or packaging requirements.

Samples should conform to market standards and/or standards filed with the agency. DPA is ready to begin receiving excipient samples for this project.

Questions and answers

The following section addresses anticipated questions about the spectral library project and the collection of samples. Answers are provided by the authors, representing DPA and IPEC.

What instruments will be used for screening excipients?

DPA plans to build two libraries, one for NIR and one for Raman spectroscopy. These are both common techniques used in library searches because their spectral features are highly sensitive to chemical structure. Both have become increasingly common in portable instrumentation due to their ability to sample through various common sampling media. Some excipients may not be suitable for both libraries because of some inherent limitations of each technique that must be taken into account when populating spectral libraries. An NIR spectrum is dependent on moisture content and particle size, for example. It contains broad and generally weak spectral features (due to sampling of overtone and combination bands). Raman features tend to be sharper and do not depend on moisture or particle size, but if a sample fluoresces, Raman spectral features can be obscured and limit the effectiveness of the library method. Some of the limitations for these two techniques can be reduced using common preprocessing techniques, such as multiplicative scatter correction or first derivative preprocessing. The results of library searches are strongly dependent on (and often enhanced by) spectral preprocessing.

How will a sample spectrum be matched to the libraries?

The typical library search consists of correlating the full spectrum of a test (unknown) sample to a reference (library) spectrum using the Hit Quality Index (HQI), shown in the following equation:

$$HQI = \frac{(Library \times Unknown)^2}{(Library \times Library)\,(Unknown \times Unknown)}$$

where the $\times$ indicates the scalar product of the two vectors. As such, library searches are aimed at gauging the full spectrum correlation of two spectra as opposed to focusing on a particular region or peak. The HQI values in the above equation range from 0 to 1.000, with 1.000 indicating a perfect match. This match is achieved when the unknown spectrum is identical to the library spectrum. FDA plans to use this concept when it implements its libraries.

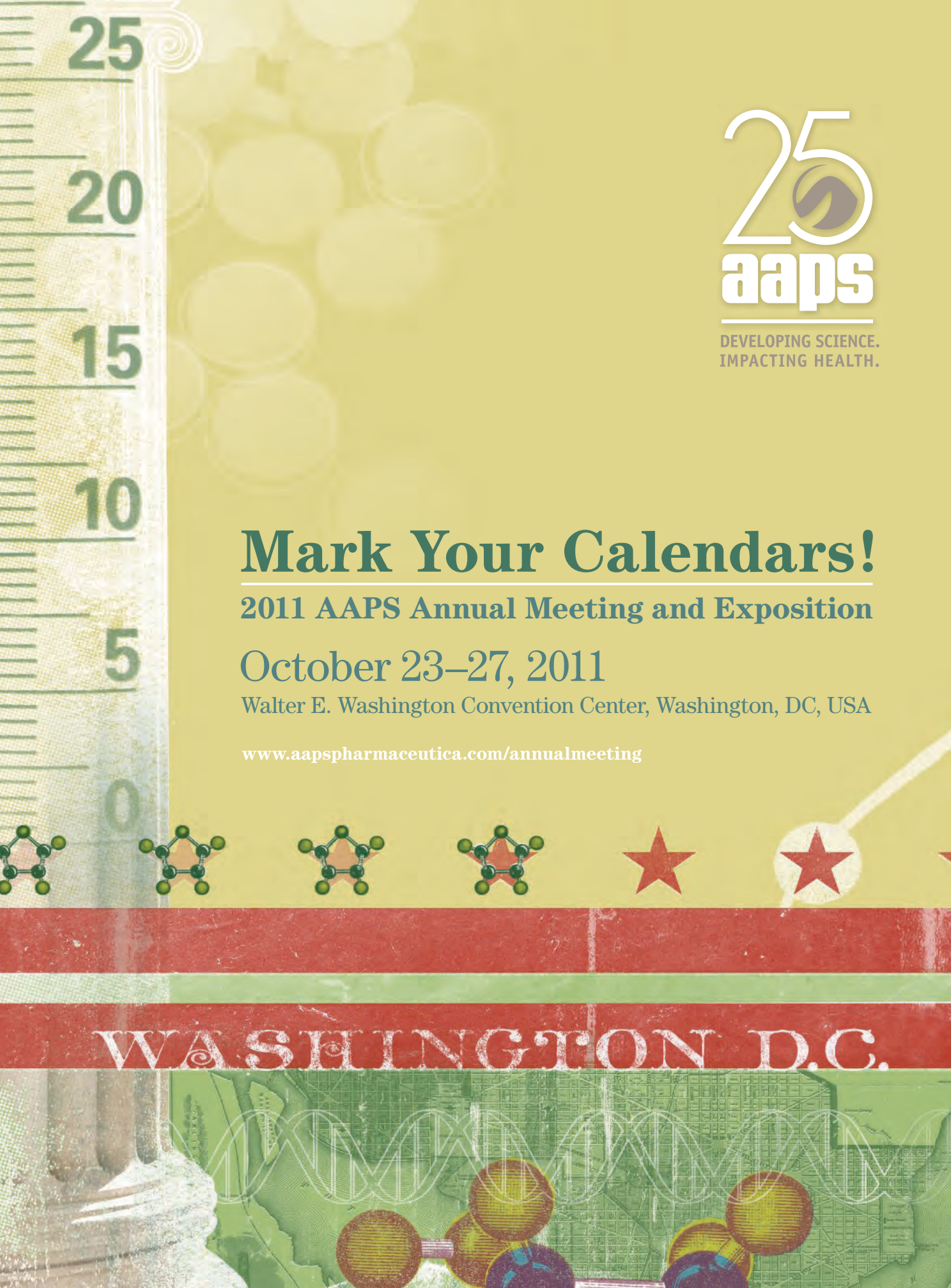

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Table I: List of priority excipients to be collected for spectral library.

Butylated Hydroxyanisole	Gelatin	Povidone
Butylated Hydroxytoluene	Glycerin	Pregelatinized Starch
Calcium Phosphate (Dibasic)	Hydroxy Propyl Cellulose	Propylene Glycol (liquid and solid)
Calcium Stearate	Hydroxy Propyl Methyl Cellulose	Shellac
Carboxymethyl Cellulose	Lactose	Silicon Dioxide
Castor Oil	Magnesium Stearate	Sodium Starch Glycolate
Cresol	Maltodextrin	Sorbitol
Croscarmellose	Microcrystalline Cellulose	Starch (Corn)
Crospovidone	Polyethylene Glycol (liquid and solid)	Stearic Acid
Ethylcellulose	Polysorbate 80	Talc
		Titanium Dioxide

Note: Samples of other excipients will also be accepted.

How many materials are expected to be in the library?

DPA has identified 166 excipients that fit in one or more of the following categories: most commonly used, most vulnerable to adulteration, or needing an update of the US Pharmacopeia monograph. From this list, FDA has narrowed down a priority list of excipients (see Table I). Once library entries for these priority materials have been obtained, the library will be deployed to field inspectors along with any other excipients that have been received. The library will continue to be expanded as additional excipients are received.

What additional types of data are being considered for this library?

Both an NIR and Raman library will be built. These libraries will contain the spectrum of each excipient. In addition to the spectrum, each entry will contain the chemical name, date added, and spectrometer details. When the library search algorithm can distinguish between different manufacturers and/or sites of manufacture of the same excipient, such further identifying information will be included.

Will the library be available to everyone?

The agency does not plan to share the library at this time. If industry and the agency see value in sharing the library in the future, FDA will conform to any provisions in the MTAs.

Will others be able to contribute to the spectral library?

FDA prefers to obtain excipients directly from manufacturers or distributors to be certain of their identity and provenance of the manufacturer and/or manufacturing site to minimize the possibility that a contaminated or subpar quality excipient is included in the library. As far as contributing spectral entries into the spectral database, FDA will not be accepting spectra.

How will the materials be used and/or evaluated?

Both Raman and NIR spectra of the excipients received will be generated without further testing or qualification of the material. As the scope of this effort is to establish a spectral library database, FDA does not plan to perform quality testing.

Would there be a time factor for the samples (i.e., would the manufacturer need to send samples every year)?

For most samples, this step would not be required. However, manufacturers could send new samples if they felt a process or raw material change could affect the spectrum of their material.

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Quality Risk Management

Principles and Industry Case Studies

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

The Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI–MTC) commissioned a risk-management working group to assemble industry case studies for the purpose of advancing the understanding and application of the International Conference on Harmonization (ICH) Q9 Guideline on quality risk management. The working group was comprised of eight representatives from industry and FDA with risk-management experience and expertise. This paper represents the outcome of the PQRI working group and provides a summary of common risk-management principles and best practices, decision-making tools to foster consistency around the use of ICH Q9, and case-study examples of risk-management applications currently in use by major pharmaceutical firms. The first of eight case studies is included with this overview article. The remainder of the case studies will appear in future issues of *Pharmaceutical Technology*.

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The harmonized Q9 *Quality Risk Management* guideline from the International Conference on Harmonization (ICH) provides an excellent high-level framework for the use of risk management in pharmaceutical product development and manufacturing quality decision-making applications (1–2). It is a landmark document in acknowledging risk management as a standard and acceptable quality system practice to facilitate good decision-making with regard to risk identification, resource prioritization, and risk mitigation/elimination, as appropriate.

Recognizing the need to propagate and expedite holistic adoption of quality risk management across the pharmaceutical industry, the Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI–MTC) commissioned a small working group of industry and FDA representatives to seek out good case studies of actual risk-management practices used by large bio/pharmaceutical firms to share with the industry at large.

The working group spent approximately one year soliciting risk-management case studies from industry peers and contacts, and ultimately reviewed more than 20 of them. Each study was graded against six multiple criteria to assess applicability, usefulness, and alignment with ICH Q9. The highest graded case studies were measured against two additional criteria to ensure a balanced mix of examples for this report. Due to the size of a well-developed risk assessment, especially when applied to a complex problem or operating area, the presented case studies in most instances represent redacted versions of the actual assessments. Nonetheless, the provided summaries are effective in demonstrating the general thought process, risk application, and use of chosen risk methods.

As a byproduct of the working group's collaboration on risk-management practices, several common principles that reflect current industry and regulatory thinking emerged. These principles are aligned with, and in some instances expand beyond, those defined by ICH Q9 and are included in this report. In addition, several risk-management reference tools used by participating firms have been included as examples.

Table I: Common risk-management tools.

Risk-management tool[1]	Description/attributes	Potential applications[2]
Basic tools		
Diagram analysis • Flowcharts • Check sheets • Process mapping • Cause-and-effect diagrams	• Simple techniques that are commonly used to gather/organize data, structure risk-management processes, and facilitate decision-making.	✓ Compilation of observations, trends, or other empirical information to support a variety of less complex deviations, complaints, defects, or other circumstances.
Risk ranking and filtering	• Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk and weighing factors and risk scores.	✓ Prioritize operating areas and sites for audit or assessment ✓ Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool.
Advanced Tools		
Fault-tree analysis (FTA)	• Method used to identify all root causes of an assumed failure or problem • Used to evaluate system/subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains • Relies heavily on full process understanding to identify causal factors.	✓ Investigate product complaints ✓ Evaluate deviations.
Hazard operability analysis (HAZOP)	• Tool assumes that risk events are caused by deviations from the design and operating intentions • Uses a systematic technique to help identify potential deviations from normal use or design intentions.	✓ Access manufacturing processes, facilities, and equipment ✓ Commonly used to evaluate process safety hazards.
Hazards analysis and critical control points (HACCP)	• Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring • Bottom-up approach that considers how to prevent hazards from occurring and/or propagating • Emphasizes strength of preventive controls rather than ability to detect • Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that critical process parameters will be met.	✓ Better for preventive applications rather than reactive ✓ Great precursor or complement to process validation ✓ Assessment of the efficacy of critical process parameters and the ability to consistently execute them for any process.
Failure-mode effects analysis (FMEA)	• Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance • Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures • Highly dependent upon strong understanding of product, process, and/or facility under evaluation • Output is a relative "risk score" for each failure mode.	✓ Evaluate equipment and facilities; analyze a manufacturing process to identify high-risk steps/critical parameters.

[1] Sample list of key risk-management tools. Others not listed here may apply for a specific application. [2] Examples only.

Scope

Risk-management principles, case studies, and supporting tools used by large bio/pharmaceutical manufacturers for effective quality oversight of product development and manufacturing operations are included in this report. Each case study notes the applicable corresponding quality system (i.e., Quality, Facilities & Engineering, Material, Production, Packaging & Labeling, or Laboratory Control) that is consistent with FDA's quality systems guidance document (3). In addition, the case studies identify the risk methodology that was used for ease of categorization, understanding, and potential application by the reader. Medical-device examples fall beyond the scope of this article, although the case studies and tools presented have relevance to device manufacturing. See the sidebar, "PQRI case studies," for details on the topics covered.

Principles and common practices

Core principles of quality risk management according to the ICH Q9 guideline include the following:

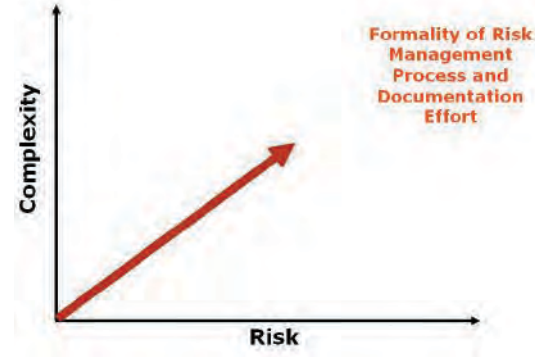
1. Compliance with applicable laws: Risk assessment should be used to assess how to ensure compliance and to determine the resulting prioritization for action—not for a decision regarding the need to fulfill applicable regulations or legal requirements.
2. Risk can only be effectively managed when it is identified, assessed, considered for further mitigation, and communicated. This principle embodies the four stages of an effective quality risk-management process as defined by ICH Q9: risk assessment (i.e., risk identification, analysis, and evaluation); risk control (i.e., risk reduction and acceptance); risk communication; and risk review.

Table II: Severity categorization.

	Category			
Severity of Consequences	**Patient Safety**	**Regulatory Compliance**	**Product Supply**	**Other**
5 – Catastrophic	Use of product will cause a serious health consequence. Patient safety is affected by product safety that is either a function of product design or a manufacturing defect.	Consent decree, product seizure, regulatoryimposed cessation of operations or equivalent.	Market stock out (patient impact) of medically significant products.	↑ Subject specific issues may warrant the consideration of other regulatory or business impacts, for example: • company reputation • cGMP practices within industry • evolving regulations Differentiation around the severity of consequences may also need to include these or other areas of interest/potential impact. ↓
4 – Very serious	↑ Use of product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Degree of seriousness is subject specific. ↓	Major observations or regulatory warning letter. Practices/facility not aligned with regulatory requirements, and there is no technical justification for approach. GMP license in jeopardy of being suspended or withheld.	↑ Market stock out (patient impact) of nonmedically significant products. ↓	
3 – Serious		Repeated and/or multiple minor observations. Practices and/or facility not aligned with current GMP expectations, but there is technical justification for the site's approach.		
2 – Important	Highly unlikely that use of product will cause an adverse health consequence.	Few minor observations/ comments. System gaps.	Product back-orders (no patient impact) resulting in active efforts to allocate supply to avoid patient impact.	
1 – Noticeable	No probability of patient impact.	One-off audit findings. Minor system gaps.	Product backorders (no patient impact) resulting in temporary shortage to wholesalers.	

Figure 1: Quality risk-evaluation pyramid.

Figure 2: Documentation level.



3. All quality risk evaluations must be based on scientific and process-specific knowledge and ultimately linked primarily to the protection of the patient. Risk assessment is based on the strong understanding of the underlying science, applicable regulations, and related processes involved with the risk under analysis. Collectively, these components should be assessed first and foremost with regard to the potential impact to the patient (see Figure 1).
4. Effective risk management requires a sufficient understanding of the business, the potential impact of the risk, and ownership of the results of any risk-management assessment.
5. Risk assessment must take into account the probability of a negative event in combination with the severity of that event. This principle also serves as a useful working definition for risk (i.e., risk represents the combination of the probability and severity of any given event).
6. It is not necessary or appropriate to always use a formal risk-management process (e.g., standardized tools). Rather, the use of an informal risk-management process (e.g., empirical assessment) is acceptable for areas that

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are less complex and that have lower potential risk. Risk decisions are made by industry every day. The complexity of the events surrounding each decision and the potential risk involved are important inputs in determining the appropriate risk-assessment methodology and corresponding level of analysis required. For less complex, less risky decisions, a qualitative analysis (e.g., decision tree) of the options may be all that is required. In general, as the complexity and/or risk increases, so should the sophistication of the risk-assessment tool used. In the same regard, the level of documentation of the risk-management process to render an appropriate risk assessment should be commensurate with the level of risk (2). See Figure 2 for details.

Risk-assessment supporting tools

A key early step in the execution of a risk analysis is to determine the appropriate risk-assessment tool, or methodology. There is no single best choice for any given assessment process, and the selection of the appropriate risk methodology should be based on the depth of analysis required, complexity of the subject risk of concern, and the familiarity with the assessment tool. Based on the industry examples reviewed by the PQRI–MTC working group, risk ranking and filtering (sometimes referred to as risk matrix) and flowcharting were the most popular tools used for basic risk-assessment activities. Correspondingly, failure-mode effect analysis (FMEA) appeared to be the most frequently used methodology for more advanced risk analysis. Some examples demonstrated

Continued on 79

PQRI case studies

The Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI–MTC) selected eight industry case studies that best embody the intent and principles of the International Conference on Harmonization Q9 *Quality Risk Management* guideline to share with industry. These examples address real-life issues, are straightforward in their application, and are designed to engender a general understanding and appreciation of the usefulness of risk-management applications in routine decision-making opportunities. Given size and complexity of the assessments, the case studies have been redacted, but still provide sufficient information to demonstrate the concept, application, and use of the fundamental risk principles used. The authors have attempted to include case studies that represent approaches that appear to be consistent with cGMPs. The content and decisions made by each risk assessment exercise represent the opinions of the authoring firm. The risk -assessment case studies are summarized below. Each case study notes the corresponding quality system (i.e., Quality, Facilities & Engineering, Material, Production, Packaging & Labeling, or Laboratory Control). Each system is consistent with FDA's quality systems guidance (3). In addition, the risk methodology used is identified.

- *Case Study 1: Defining Process Space.*
  System: Other (product development). Risk tool: Failure-mode effects analysis (FMEA).
- *Case Study 2: Functional Equivalence for Equipment Replacements*
  System: Facilities & Engineering. Risk tool: Fault-tree analysis (FTA).
- *Case Study 3: Facility Biocontainment Inactivation*
  System: Quality. Risk tool: Hazards analysis and critical control points (HACCP.)
- *Case Study 4: Process Deviation Analysis (Empty Capsules)*
  System: Quality. Risk tool: FMEA.
- *Case Study 5: Nonsterile Facility Cleaning Requirements*
  System: Quality Risk tool: Decision tree and risk matrix.
- *Case Study 6: Packaging Line GMP Optimization*
  System: Packaging. Risk tool: FFEA (FMEA modified).
- *Case Study 7: Pack-Out Remedies to Minimize Contamination and Exposure*
  System: Facilities & Equipment. Risk Tool: Evaluation table / Hazard operability analysis (HAZOP) elements.
- *Case Study 8: Internal GMP Auditing*
  System: Quality. Risk tool: Risk Ranking & Filtering.

Each case study is organized according to the following general sequence:

Background. A brief summary is provided of the area of required risk assessment.

Risk question. The first step in the quality risk management (QRM) process is to develop and agree upon the risk question. In the development of the question, it is important to first consider whether there is any potential impact of the proposed actions to the patient. Evaluation of risks, when applicable, should ultimately be linked to the protection of the patient. Clearly defining the risk question facilitates selection of the appropriate tool, identifies relevant data, information and assumptions, assists in the identification of resources, responsibilities and accountabilities, and ensures that appropriate focus on the business objective is maintained.

Risk-assessment method. The selected risk-assessment method or tool will be used to organize data and explain what steps can be taken to reduce or control risk, and thereby, help to make appropriate decisions. In the selection of a risk tool, it is recommended that the user evaluate the QRM process and select the simplest tool available to support the process.

Risk assessment (identification, analysis, and evalution). The objective of risk identification is to develop a comprehensive analysis to include all applicable operations. At this stage of the QRM process, care should be taken not to exclude operations that may be perceived as having low risk, without fully evaluating the actual and associated potential influences and risks involved. The risk-analysis stage estimates the potential harm(s) associated with each potential risk. The analysis may be qualitative or quantitative in nature, or a combination of the two.

Risk control . During the risk-control stage of the QRM process, a decision is made on which risks, if any, require mitigation. Necessary actions are taken to reduce or avoid all prioritized risks, as appropriate and practical.

Risk documentation and communication. Communication of the QRM process should integrate key stakeholders. Ensuring that key stakeholders are engaged in the data-collection and decision-making processes maximizes the probability of organizational buy-in and support. The output of the process and associated risk analysis justifying the approach should be documented and endorsed by the site quality unit. Additionally, this information should be communicated to stakeholders for their information and to ensure their support.

Risk review. Appropriate systems should be put in place to ensure that the output of the QRM process is periodically reviewed, as appropriate, to assess new information that may impact the original risk-management decision. Examples of changes that may affect risk of site operational systems include: changes to control systems, changes to equipment and processes, changes in suppliers, and organizational restructuring.

The first case study appears on the following pages. The remaining case studies will appear in the next several issues of *Pharmaceutical Technology.*

Defining Process Design Space

A Risk-Management Case Study (Part 1)

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

This case study on defining process design space is the first of eight in a series put together by the Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI–MTC) risk-management working group. The series is meant to advance the understanding and application of the International Conference on Harmonization (ICH) Q9 *Quality Risk Management* guideline by providing actual examples of risk-management assessments used by the bio/pharmceutical industry. The introductory article appears on page 72 of this issue. The remainder of the case studies will appear in future issues of *Pharmaceutical Technology*.

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Risk assessment of the manufacturing process is a key activity in product development, especially as a supportive tool in quality by design (QbD). In this case study, a drug product was formulated with different variants, each with a different dissolution profile ranging from slow to fast. While an *in vitro–in vivo* correlation (IVIVC) evaluation was not possible due to product-specific pharmacokinetic factors, the profiles of all of the formulations were similar. The dissolution method was already known to be over-discriminatory and the slowest dissolution profile from the range of formulation variant studies was set as the slowest dissolution profile acceptable. This profile would serve as the surrogate test for the quality of the clinical product in processing studies. In other words, the design space for clinical quality would be a product with a faster dissolution profile than the slowest variant. To ensure a full understanding of all potential influences to the design space, a full risk assessment of the manufacturing process was conducted to ensure that areas of greatest risk were appropriately considered and controlled.

Risk question and risk-assessment method

The risk question developed for the subject case study is: *What are the critical input and processing variables for the product that would affect the product quality based on the design space?*

A manufacturing process for a drug product usually consists of many steps, each with potentially multiple variables requiring evaluation. The selected risk-assessment method must produce a quantitative output that describes the level of risk relative to other risks being assessed. As an aid to a likely complicated risk assessment effort, the resulting data should also be organized in such a way that that a simple visual summary can be produced. Failure-mode effect analysis (FMEA) was selected for this case study.

Risk identification

The risk-assessment team assigned to this initiative first prepared a list of all operations and associated supporting systems that had potential impact on product quality. During this stage of the quality risk management (QRM) process, no processes were excluded simply because the process was perceived as "low risk" (see Table I).

Table I: Quality risk management output.

Risk area	Failure mode	Failure effect	Risk analysis			
			P	S	D	RPN
RAW MATERIALS						
Drug substance	Changes in particle size or properties (*e.g.,* shape, surface energy, bulk properties)	Changes in dissolution performance, thus impacting on clinical performance	4	5	5	**100**
Excipients	Increasing the level of binder	Slow tablet disintegration leading to altered clinical performance	4	5	5	**100**
	Decreasing the level of disintegrant	Impeded tablet disintegration leading to altered clinical performance	4	5	5	**100**
	Magnesium stearate variability, leading to impeded wetting of drug particle	Changes in dissolution behavior leading to altered clinical performance	3	5	5	**75**
	Variability in amount of diluents or properties within specified grade	Changes in granule properties resulting in altered disintegration/dissolution profile	2	5	5	**50**
PROCESS						
Dry mixing	Insufficient mixing; poor blend uniformity	Large range of active ingredient content throughout the batch	2	3	4	**24**
Wet granulation	Failure to control granulation end-point; Over-granulation	Decreased granule porosity, decreased water ingress, and decreased dissolution rate. Adverse effect on clinical quality	4	5	5	**100**
	Excessive water added or holding the wet mass for significant time before drying	Decrease in disintegrant performance; wicking and swelling during wet massing. Decreased dissolution rate and consequent adverse effect on clinical performance.	3	5	5	**75**
Dry milling	Incorrect dry milling parameters (*e.g.* impeller speed, screen size)	Effect on granule size leads to altered dissolution and adverse effect on clinical performance	3	5	5	**75**
Lubrication	Blending time too long, leading to hydrophobic coat of lubricant around granules	Decreased dissolution rate leads to adverse effect on clinical performance	3	5	5	**75**

Note: P is probability; S is severity, D is detectability, and RPN is risk product number.

Risk analysis and evaluation

The risk-analysis stage of the QRM process estimates the potential harm(s) associated with each potential risk. The analysis may be qualitative or quantitative in nature, or a combination of the two.

In this case study, the analysis used was quantitative. The risk score or risk product number (RPN) was determined by multiplying the scores for probability, severity, and detectability, as shown in the following equation:

$$\text{RPN} = \text{probability score} \times \text{severity score} \times \text{detectability score}$$

where the ranking definitions for probability, severity, and detectability were developed prior to commencing any actual assessment (see Table II). After the risk areas were identified, subject-matter experts evaluated each risk area and listed corresponding failure modes and failure effects for each risk area. Subsequently, probability, severity, and detectability were determined using the scoring criteria in Table II. The results were collated and reviewed to ensure consistency and accuracy. The final output was published for risk prioritization.

Each line item from the assessment was ranked as either a low, intermediate, or high risk, depending on the calculated RPN value. A RPN of < 40 was considered a low risk; a RPN of 40–99 was identified as an intermediate risk; and a RPN of ≥ 100 was defined as a high risk. Risk rankings took into consideration the overall RPN value as well as how significant the issue under assessment was to the development of the product. In many cases, mitigating the larger RPN issues also resulted in a decrease in the calculated RPN for areas with lower identified risks. To facilitate understanding and management of the results defined by Table I, a color-coded chart was developed to correlate risk-assessment results to anticipated tablet quality, categorized by specific unit processes. By summarizing the results in this manner, the project team was able to see and communicate how the identified risks were inter-related and prioritized (by RPN) for risk mitigation.

Risk control

Assessed risks were reduced by identifying the unit operations or procedures where the RPN was calculated above a certain threshold and developing corresponding risk-mitigating strategies to lower the overall calculated risk level. This calculated RPN value was a relative number based on other assessed risks, and was developed using a set of predefined definitions on severity, probability and detectability. After implementing mitigating actions to reduce the perceived high risk areas, the RPN values were recalculated to ensure that the projected risks were appropriately reduced.

Table II: Scoring scheme for probability, severity, and ability to detect.

Probability	Score
1/>10000	1
1/1000	2
1/100	3
1/10	4
1/<10	5
Severity	**Score**
Deviation	1
Re-analysis, passed	2
Rejected sub-batch or batch	3
Stop in production flow	4
Product recall	5
Detectability	**Score**
Before unit operation	1
During unit operation	2
During subsequent unit operation(s)	3
Finished-product testing	4
Detected by customer	5

Risk documentation and communication

The risk analysis was reviewed by management and experts in QRM assigned to the project. The knowledge gained through this risk assessment was shared with the employees at the company's other development sites as well as externally through a series of presentations at industry forums. In addition, the lessons learned from this risk assessment have been incorporated into current development projects and will be institutionalized for future use.

Risk review

In following the company policy for quality and quality systems, a report describing the rationale, risk-assessment process, action plan, and conclusions were forwarded to the appropriate internal quality groups for future follow-up (e.g., audit, preapproval inspection, risk analysis). To follow the feedback loop as recommended in ICH Q9, work was carried out to mitigate the risk of the items with high RPNs (e.g., action plan implementation). After this work was completed, the group reviewed the results of the mitigation actions and some batches manufactured after the risk assessment and convened a second quality risk assessment focusing on the areas with high RPNs. Other risk areas with initial lower RPN values were also assessed to determine any additional impact (positive or negative) resulting from mitigating actions taken for the highest prioritized risk areas. The results of this follow-up were published in the same format as Table II and distributed to the stakeholders. A third review was carried out after the implementation of the risk mitigation actions discussed above. This third check, somewhat removed from the initial assessment and mitigating efforts, was performed to further ensure that the conclusions and actions from the risk assessment were correct. **PT**

Continued from 76, Quality Risk Management

the power of combining tools to help with more complex analysis. For example, fault-tree analysis (FTA) or a fishbone diagram can be used to initially scope and evaluate the fault modes of a particular problem and be used to feed a hazards analysis and critical control point (HACCP), or a similar tool to evaluate overall system control and effectiveness can be used. Table I provides a list of generally well-recognized risk-management tools.

Each risk subject and assessment warrants consideration of the applicable descriptors of potential risk and related consequences. Ideally, firms should establish a guidance document ahead of any risk analysis, such as the one provided in Table II, to help guide the risk-assessment process and provide for consistency in decision-making company-wide.

Risk trainers. In assembling this collection of case studies, the authors recognized the benefit of providing industry with additional background on core risk methodologies. Training tools for the application of risk ranking and filtering, FMEA, FTA, and HAZOP are available online with the web version of this article at PharmTech.com/PQRIstudies. These tools are meant to facilitate greater familiarity with the risk methodology used in each corresponding case study.

Conclusion

The PQRI–MTC Risk Management Working Group solicited and formatted a series of best-practice case studies aligned with ICH Q9 principles. The collected case studies demonstrate that there is a wide range of applications for the use of structured risk-management analysis to facilitate effective quality-decision activities. The studies demonstrate the baseline needed to choose the appropriate risk methodology for the targeted need, taking into account the degree of complexity and risk involved for the specific subject of concern. It is equally important to predefine the potential resulting risk categorizations so as to not be influenced by the assessment results in defining appropriate response actions. Finally, once risks have been appropriately assessed and prioritized, clear risk-mitigating actions must be defined, communicated, implemented and monitored for effectiveness.

References

1. FDA Global Harmonization Task Force, "Implementation of Risk Management Principles and Activities within a Quality Management System" (Rockville, MD, 2000).
2. ICH, Q9 Quality Risk Management, 2005.
3. FDA, *Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations* (Rockville, MD, 2006).
4. FDA, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites–A Pilot Risk Ranking Model," (Rockville, MD, 2004). **PT**

JONATHAN EVANS/PHOTODISC/GETTY IMAGES

PharmTech.com/outsource

Offsetting Budget Cuts

Gregg Brandyberry

Better strategies and practices in sourcing and procurement can contribute to the bottom line.

For several years, Big Pharma has been cutting programs and reducing headcount as a result of mergers and acquisitions and overall cost-cutting efforts. According to industry estimates, approximately 50,000 pharmaceutical industry employees lost their jobs in 2010, and 300,000 have been let go in the past 10 years (1). Many reasons are behind these cuts: a decline in traditional research and development productivity, tougher regulatory hurdles, a plethora of government and formulary pricing controls, and significant patent expiry of major blockbuster drugs.

Now, more than two years after the economic meltdown, the industry understands that prosperity is not around the corner. What many call the "New Normal," characterized by slower growth, tighter credit markets, a more conservative approach, less money available for investment, and tighter financial regulations, has become the new operating reality.

It doesn't have to be all doom and gloom, however. Even in the best-run organizations, there is an untapped source of cash from what I like to call "creating your own stimulus by buying items and services better." In many companies, the cost of purchased items and services (i.e., the money paid to suppliers) is equal to between 30–70% of total company revenue. In the pharmaceutical industry, this cost is typically between 30 and 50%. What I've come to understand is that regardless of how good or how bad a company is at buying products and services, there is still plenty of cash to extract from its costs. Three methods—spend segmentation, better specifications, and online reverse marketplaces—can improve results.

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Spend segmentation. By not applying the appropriate sourcing strategy, a company may pay between 10% and as high as 70% more for products and services, based on my experience. This differential exists because of the strategy or lack of strategy that is in place for a certain purchase. Figure 1 identifies four types of supplier relationships by such attributes as ease of buying, supply-market competitiveness, uniqueness, and strategic importance. A buyer's strategy needs to be in the right quadrant to ensure that a company is paying the right price, producing the right total cost, and getting the best value associated with a particular product or service.

For example, if a company is making a purchase where the supplier maintains the power in the relationship (i.e., the "critical" quadrant), the buyer is paying an absolute premium. Typically, less than 10% of a company's spend will be designated as "critical," according to my experience. Companies with poor purchasing practices, however, often allow suppliers to act as if they were a natural monopoly. A purchaser should review its spending to move supplier relationships from the "critical" quadrant to "strategic" or better yet to "leverage" positions (see Figure 1). My experience suggests that on average, only 20% of spend is truly "strategic," and most of what is purchased can be highly leveraged among multiple suppliers.

Better specifications. Many factors determine how much to pay for a good or service. In simple terms, supply is what is available, and demand is how much is being requested. Consumption is how much is being used at what rate, and specification is what constitutes a product or service. The interactions of these variables are the main drivers of price paid.

Figure 1: Spend segmentation categories based on customer–supplier relationships.

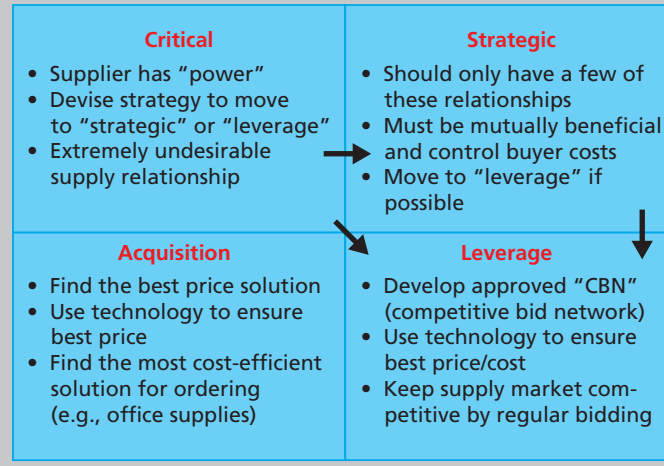
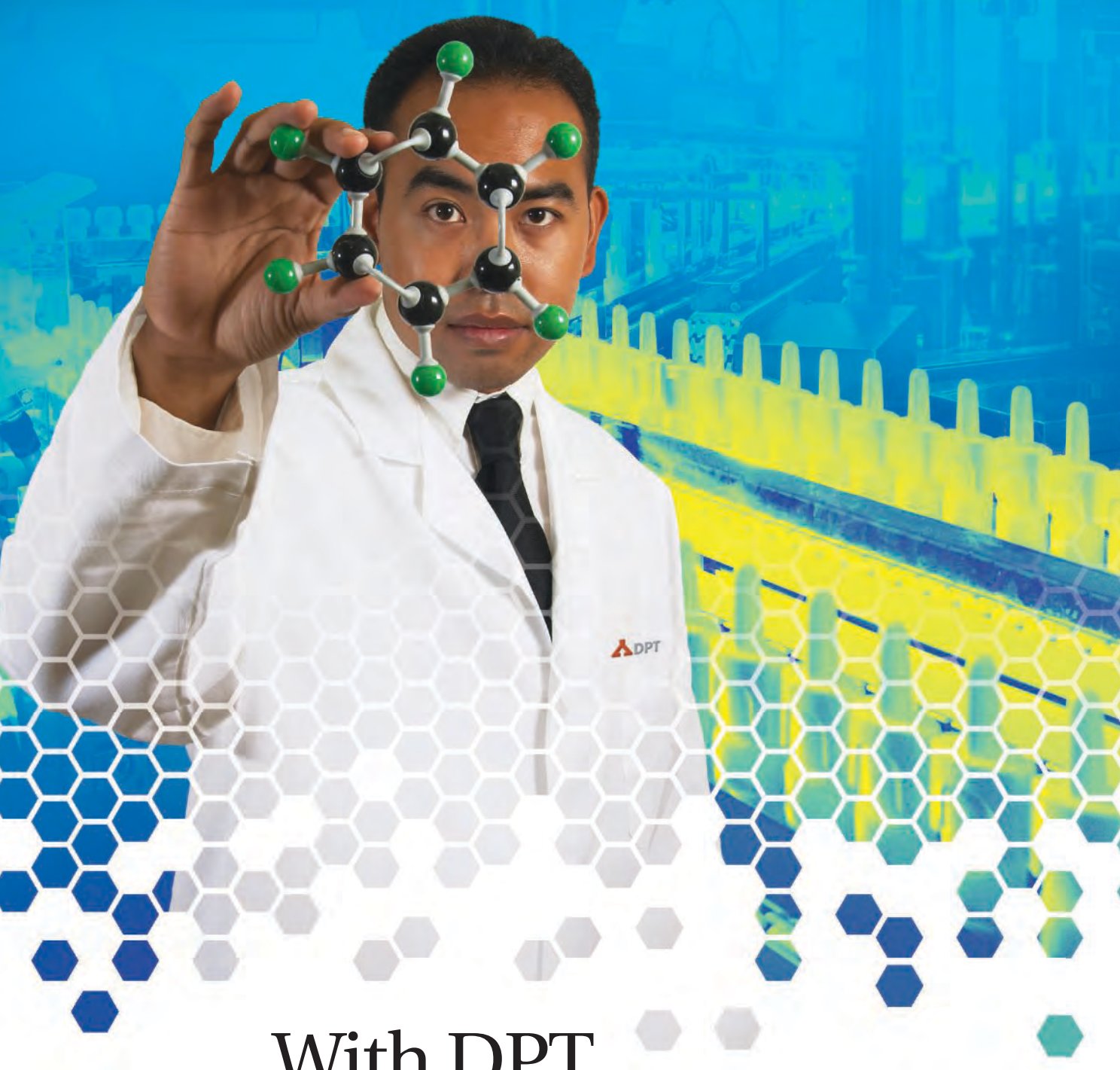


FIGURE 1 IS COURTESY OF THE AUTHOR



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Once spending is properly segmented per Figure 1, four focal points determine the price paid. A company's strategy affects its ability to pay less, to use less, to use something else, or not to use at all. Take a close look at specifications and carefully review the requirements. In many cases, a company will find individual requirements that are "over spec'd" or not needed at all, which lead to significant and unnecessary costs. Additionally, consumption can often be reduced by making the user community aware of the total costs involved and by policies that control overall usage, particularly for indirect items and services.

Online reverse marketplaces. Think about how a company buys. It is probably one of the following scenarios. The simplest is calling the supplier and accepting the price being quoted. Then there is the "haggle" method, same as the first method, but with some pressure applied to get a lower price. Then more sophistication with the "competitive bid policy," in which the buyer typically gets three bids before making a selection. Another method is to do additional negotiation after getting the three bids, an interesting approach, but it still may fall short in securing the best possible terms.

A reverse auction, a transparent and dynamic bidding model, is different. All sellers are bidding on the exact same item or service. When using this method, the buyer must have good specifications or requirement documents available to all sellers as opposed to the haphazard way requirements are given using some of the other traditional methods. Because the buying event has great transparency, sellers can see if their pricing leads or lags. The buyer does not have to select the lowest bidder and may weigh other factors in the purchasing decision. Reverse auctions drive pricing to what the market will bear at any given time against various seller independent variables.

Until recently, the technology required to conduct reverse auctions was costly, required considerable employee training, and presented certain internal and some external barriers for implementation. These barriers, however, are eroding. The premier reverse auction marketplace, FedBid, used by the federal government for 10 years, is now available for commercial use and offers a procurement model for commodity products and basic services. The marketplace has over 50,000 qualified suppliers. More than 50,000 "buys" were conducted in 2010 with savings ranging between 5 and greater than 50%. There is no cost to the buyer for using the technology, which is web-browser-based. The winning seller pays a modest 3% transaction fee and is billed by the marketplace operator 60 days after the buying award is made. If the product is not currently in the marketplace, the marketplace operator will at, no charge, find the right sellers and even train a company's existing suppliers so they can compete on a regular basis in the marketplace. Reverse auctions can be good for buyers and sellers. Buyers save money, and sellers gain more opportunities to win business. Reserve auctions, along with the other sourcing practices discussed, are potential drivers for value creation.

Reference

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Meggle to Begin US Production

Meggle Business Group Excipients and Technology, a leading manufacturer of excipients for the pharmaceutical industry, will start operating its first US production site in Le Sueur, Minnesota, in September 2011. The new site will eliminate many bureaucratic and customs obstacles for US buyers and help accelerate transactions.

Meggle gives special priority to the sustainability of all of its operating processes, according to a press release. The company will take measures to ensure that the new plant is environmentally friendly, especially because it is located in a rural area.

CML Launches Active Ingredient at New Facility

FDA conducted the first inspection of Cambridge Major Laboratories's (CML) newest facility in Germantown, Wisconsin. Within two months of the successful preapproval inspection, FDA approved the product, and the company subsequently launched commercial production of an active pharmaceutical ingredient at the facility.

FDA conducted a preapproval inspection and a general quality-systems inspection of both of CML's sites. The first FDA inspection at the new, large-scale facility was the seventh inspection of CML during the past nine years. The approval will enable CML to continue to add employees and services to support its ongoing growth. Currently, CML manufactures more than 12 commercial products, including new drugs, generic substances, and medical-imaging agents, at its sites.

Vetter Adds Lyophilization Capacity

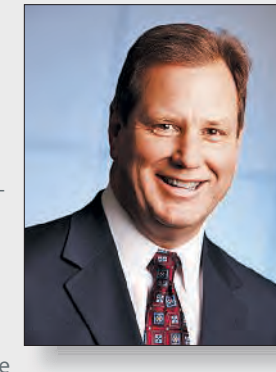
Vetter, a specialist in aseptic filling, installed three additional state-of-the-art lyophilizers at the company's Ravensburg Vetter South facility. The installation nearly doubles Vetter's number of freeze dryers. The site will now be able to produce as many as 24 million lyophilized units annually. The new equipment increases the number of lyophilizers at all Vetter facilities by 30%. The company made the investment to meet anticipated future demand for aseptically filled biologics and other sensitive compounds, which often require lyophilization to prolong shelf life and potency. Vetter introduced lyophilization services in 1981 and uses dual-chamber technology to help reconstitute lyophilized compounds.

Chemsultants Celebrates 25th Anniversary

On July 15, 2011, Chemsultants International will mark the 25th anniversary of the founding of the company. Richard P. Muny started the company in 1986 as a pressure-sensitive adhesive consultancy, and it has become a product and service provider to industries worldwide. Chemsultants now includes two companies, Chemsultants International and ChemInstruments, focused on adhesives, specialty coatings, polymers, and materials. Chemsultants International provides services including physical and analytical testing, process development and optimization, and small-scale manufacturing of web-coated materials.

Q&A with

Steve Strickland, *general manager of Sensient Pharmaceutical Coating Systems*



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

Strickland:
A major challenge is maintaining continuous scientific innovation to meet the product demands of our customers. We are constantly looking for opportunities to expand our technical expertise and service either through internal development or acquisition.

I think that the consolidation within the pharmaceutical industry we serve will continue to play a role in our growth. Consolidation often brings personnel change, accompanied by shifts in the direction of research and development. We need to evolve along with our customers based on their changing needs.

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

Strickland:
Our primary method of staying on top of industry developments is listening to our customers. Also, trade shows and trade publications are an excellent source of emerging industry trends, and we'll continue to rely on them.

PharmTech:
Do you see a new industry trend emerging?

Strickland:
Yes, the trend toward globalization of our industry continues to gain momentum. For example, the emergence of global markets, the multinational presence of pharmaceutical companies, and the location of manufacturing sites around the world demand an increased knowledge of the accompanying regulatory requirements.

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

Strickland:
They demand high product quality. In an industry that is constantly under scrutiny, our customers demand excellence in the quality and performance of our products.

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In general alkaline cleaners are preferable to acidic cleaners for pharmaceutical residues. However, for cleaning residues such as insoluble hydroxides, metal oxides, carbonates, bicarbonates, starches, amphoteric proteins, amines and alkaloids an acidic cleaner is recommended. See related whitepapers at www.Alconoxwhitepaper.com/cGMP				
Below is a quick reference table for cleaners to be used in the pharmaceutical industry.				
Alkaline High pH detergents are generally used for equipment cleaning	**Application:**	**Phosphate:**	**Powders:**	**Liquids:**
	Manual/Ultrasonic	Phosphate	Alconox	N/A
	Manual/Ultrasonic	Phosphate Free	Tergajet	Liquinox
	Machine/Spray CIP	Phosphate	Alcojet	Detojet
	Machine/Spray CIP	Phosphate Free	Tergajet	Solujet
Acidic/ Low pH Cleaners	Manual/Ultrasonic	Phosphate Free	N/A	Citranox
	Machine/Spray CIP	Phosphate Free	N/A	Citrajet

The Alconox Mission

Alconox, Inc. is dedicated to being the critical cleaning experts. We manufacture quality detergents made in the United States and provide outstanding technical service to the scientists and engineers with precision cleaning needs.

Where We Came From…

The ALCONOX brand was introduced in 1941 for use in hospitals and laboratories as a hard surface cleaner that cleaned without interfering residues. This innovative and desirable technology led to the rapid acceptance of ALCONOX, and to the formation of Alconox, Inc. in 1946. We have expanded continually increasing into new markets with new brands. The year 2011 marked our 65th year as a successful privately held corporation.

The Benefits of Aqueous Critical Cleaning

The benefits of employing aqueous cleaning in pharmaceutical manufacturing are numerous. Virtually any pharmaceutical manufacturing equipment from tablet press to a stainless steel mixing tank can achieve their defined critically clean criteria using aqueous cleaning. Typically aqueous cleaners are formulated to ensure maximal cleaning performance by using key ingredients such as surface active agents (surfactants) that are excellent wetting agents that allow the cleaning solution to penetrate into crevices while getting under soils to allow for removal. Often very dilute solutions of aqueous cleaner effectively removes even worst case substances off a variety of hard surfaces including stainless steel, glass, plastic or porcelain.

The Pharmaceutical Advantage

With about 50 years of experience in the pharmaceutical industry and technical knowledge at your fingertips. Alconox, Inc. is the logical choice for your pharmaceutical cleaning and cleaning validation needs. We provide the detergents and industry information to be successful. See the table above for typical cleaning in the pharmaceutical industry.

65 YEARS
1946-2011
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Critical Cleaning Experts

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3M Drug Delivery Systems

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3M Microneedle Technology takes delivery beyond traditional injection.

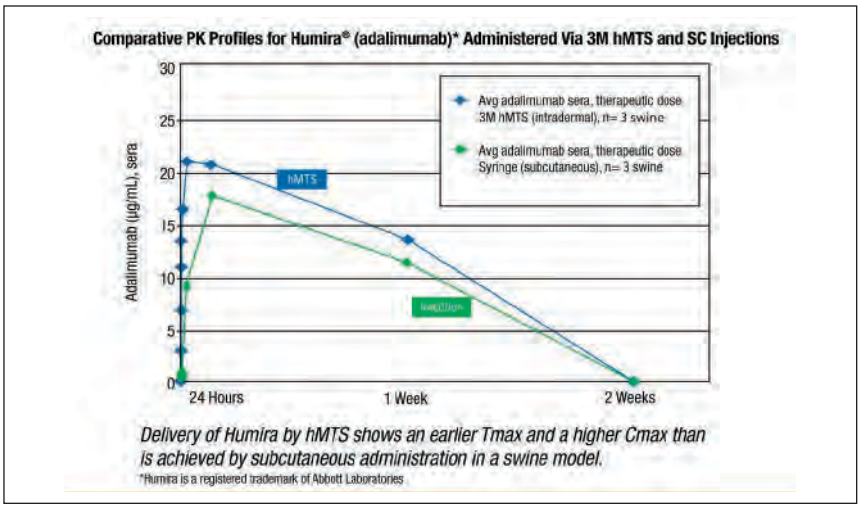
3M Microstructured Transdermal Systems (MTS) deliver a wide range of APIs, including proteins, peptides, vaccines and difficult to deliver molecules. 3M MTS leverages core 3M technologies to combine the efficiency of a syringe with the convenience of a transdermal device.

MTS delivers significant benefits compared to injections that for some drugs and vaccines may include improved delivery efficiency, quicker onset of action and the potential to achieve similar efficacy using less drug. Additionally, MTS helps improve compliance through easy self-administration with minimal discomfort.

With up to 0.3 mg capacity, the solid microneedle system (sMTS) utilizes 375-1300 solid microneedles per cm^2, 150-700µm tall, each coated with drug or vaccine and integrated into a small, wearable device. 3M precision coating technology is used to uniformly apply the drug or vaccine to the tips of the microstructures. Upon application, the microneedles penetrate the stratum corneum and remain there while the drug or vaccine is released from the microneedles and diffuses into the tissue. The device wear time is short, ranging from 30 seconds to 10 minutes. Because the drug or vaccine is in the dry state, sMTS has the potential to enhance stability for some drugs, allowing room temperature storage.

With up to 2 mL capacity, the hollow microneedle system (hMTS) utilizes 18 hollow microneedles

per cm^2, approximately 950µm tall, integrated into a small, wearable device designed for efficient intradermal delivery of liquid formulations. Upon application, the microneedles penetrate the skin while small channels allow for fluid flow from the device into the skin, with wear time ranging from 2 to 20 minutes. hMTS is uniquely suited for high volume intradermal infusion and provides the potential for improved pharmacokinetics relative to subcutaneous injection for a variety of drugs, including monoclonal antibodies.



3M DRUG DELIVERY SYSTEMS
TRANSDERMAL SYSTEMS

Some see an impossibly large molecule.

WE SEE A PERFECT FIT.

3M microneedle technology delivers the widest range of API's in a transdermal format scalable to your needs.

3M Microstructured Transdermal Systems (MTS) combine the efficiency of a syringe with the convenience of a transdermal patch.

- Local or systemic delivery for a wide variety of molecules, including proteins, peptides and vaccines
- Microneedles bypass barrier properties of stratum corneum with delivery efficiency that matches or exceeds injection
- Provides competitive differentiation and lifecycle management solution

3M's team of formulation, development and manufacturing experts are ready to ensure your needs are met from clinical to commercial scale. **Find out more at www.3M.com/MTS.**

US: 1 800 643 8086
UK: 44 (0) 1509 613626
ASIA: (65) 6450 8888

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ENABLING YOUR SUCCESS.

3M

ADVERTORIAL

Asahi Kasei

www.ceolus.com

Asahi Kasei is a global supplier of microcrystalline cellulose (MCC) and other multi-compendial pharmaceutical excipients. Through our intensive research and development efforts, the company provides products that offer innovative solutions for solid dosage formulations for both small molecule pharmaceuticals and biopharmaceuticals. We also support our products with excellent and responsive technical service.

The **Swelstar**™ group of pregelatinized starches are Asahi Kasei's newest excipients, jointly developed with Sanwa Cornstarch.

Swelstar MX-1, developed for gel-matrix tablets, achieves pH-independent sustained release under high ionic strength conditions and is alpha- amylase resistant.

Swelstar PD-1 and **Swelstar WB-1,** designed as superdisintegrant and wet binder, respectively, have characteristics that make them uniquely suited for their applications.

Ceolus®KG-802 and **KG-1000** (MCC with distinctive rod-form particle shapes) are ideal for tableting poorly compactible drugs or coated granules. They are very effective for reducing tablet size, improving hardness and friability, increasing operating rates and lowering compression force.

Highly compactable MCC KG-802

Ceolus UF-711, another of Asahi Kasei's specialty MCC grades, combines superior compactibility with good powder flow due to its relatively round and porous particles. UF-711 is designed especially for direct compression with gravity feeders.

Celphere®, a superior alternative to sugar spheres, is a 100% microcrystalline cellulose spherical seed core that is capable of reducing agglomeration during drug layering and film coating to produce higher yields and more precisely control drug release.

PC-10 is a high-swelling pregelatinized starch with an extremely low water-soluble content. It is an ideal stabilizer for moisture-sensitive APIs.

MCC spherical seed cores: Celphere CP-305

Trehalose, a non-reducing disaccharide, combines taste-masking with low reactivity and stability.

Kiccolate, croscarmellose sodium (non-GMO), is a widely used and accepted superdisintegrant.

AsahiKASEI

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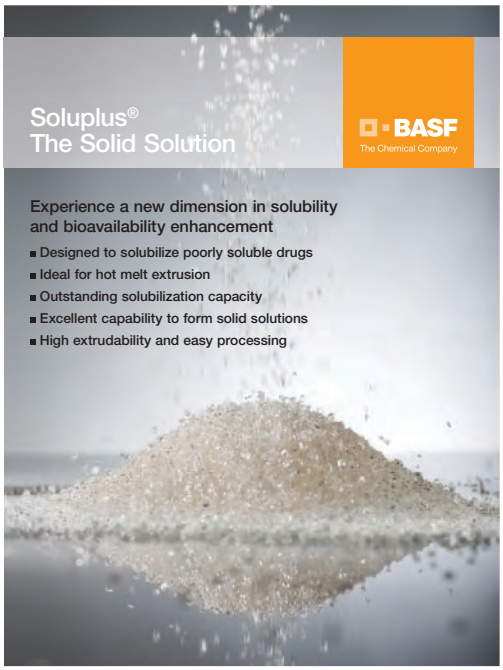
BASF Corporation

www.pharma-ingredients.basf.com



BASF Pharma Ingredients & Services

BASF produces and markets a broad range of active ingredients and excipients, as well as exclusive synthesis services for the pharmaceutical industry. Innovative chemistry, efficient manufacturing and a global presence help make BASF a leading supplier to the pharmaceutical industry.

Within the excipients business, BASF provides formulation expertise and experienced technical support. BASF's services in the production of medicines encompass the supply of a vast range of high-performance excipients such as binders and disintegrants from the Kollidon® family, coating polymers marketed under the Kollicoat® brand, and numerous other substances, including solubilizing agents. All products are manufactured fully in accordance with cGMP guidelines (cGMP stands for current Good Manufacturing Practice).

BASF's latest innovation in excipients

Soluplus® is an innovative pharmaceutical excipient which enhances the solubility of poorly soluble drugs and so increases their bioavailability, i.e. the absorption of the drugs in the body. The new product is ideal for innovative process technologies such as melt extrusion.

More information is available on our website at www.soluplus.com.

Kollicoat® IR Coating Systems: Distinctive coloring, robust and rapidly soluble: the new BASF tablet coating system enables individual, on-site production of tablet coatings in countless shades from only seven basic colors. A combination of the tried and tested water-soluble BASF IR film former Kollicoat® with a new production process and novel color concept makes tablet coating production more efficient.

More information is available on our website at *www.coating-systems.basf.com*.

Ludiflash® is an excipient specially developed for orally disintegrating tablets (ODT) that provides a smooth and creamy mouth feeling. Tablets disintegrate in the mouth, even without water, thus allowing patients to take tablets more easily and discreetly for rapid relief of symptoms. It is designed for direct compression on standard high-speed tableting machines, which saves manufacturers time and money.

More information is available on our website at *http://www.pharma-ingredients.basf.com/ludiflash*

To find out more, simply contact us via e-mail at pharma-ingredients@basf.com or visit us at *www.pharma-ingredients.basf.com.*

BASF
The Chemical Company

ADVERTORIAL

BD Medical – Pharmaceutical Systems

www.bd.com/pharmaceuticals

Corporate Description

BD Medical – Pharmaceutical Systems provides high-quality, customized, clinically-proven drug delivery systems and technologies to help pharmaceutical and biotechnology customers' injectable drugs reach their full potential.

BD has over 100 years of experience in manufacturing and processing technology for parenteral drug delivery systems and has developed an in-depth understanding of the pharmaceutical industry's requirements. BD has leveraged this experience when developing advanced drug delivery systems that span from small scale clinical through large scale commercial programs.

BD offers a selection of products, including glass and plastic prefillable syringes and a variety of systems for the self-administration of injectables. With a broad scope of innovative systems and services, BD Medical - Pharmaceutical Systems provides pharmaceutical companies with support and resources to help them achieve their goals.

BD is committed to building partnerships to develop product solutions that meet evolving customer needs by leveraging innovative technologies, extensive global manufacturing and advanced technical and scientific expertise.

Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond.

ADVERTORIAL

Cambridge Major Laboratories

www.c-mlabs.com

About CML
Cambridge Major Laboratories (CML) is a leading global chemistry outsourcing partner to the pharmaceutical and biotechnology industries. CML produces pharmaceutical intermediates and Active Pharmaceutical Ingredients (API), from early preclinical development to commercial manufacture. Operating from FDA-inspected facilities in the US and Europe, CML is organized along five key integrated Centers of Excellence:

Process Chemistry
We understand that maintaining a high ratio of PhD scientists is essential to provide rapid and reliable chemistry services to support early preclinical quantities through full production at plant scale. Because our PhD scientists follow the projects from the lab into the plant, we have the expertise to troubleshoot any possible issues that may arise during the scale-up phase. Whether you need a synthetic route completely developed, or can provide us a fully developed process, we'll get the job done safely, efficiently, and on specification.

API Manufacturing
CML's state-of-the-art manufacturing facilities meet global regulatory requirements, GMP compliance standards, and are FDA inspected and approved. By leveraging the range of equipment in our manufacturing facilities, our pharmaceutical contract manufacturing services can support the drug discovery process through API synthesis for all stages of clinical trials. We conduct GMP manufacturing of APIs from grams to multi-ton quantities.

Solid State Chemistry
CML combines its leading position in process chemistry with solid state chemistry to provide clients the most optimal solutions ranging from polymorph screens to optimizing crystallization conditions along a synthetic pathway. In a world where development timelines are continually squeezed, there is an opportunity to optimize the drug substance development path by having the solid state chemist work in close collaboration with the process chemist at every step of the synthesis pathway.

Analytical Services
CML provides a wide variety of analytical support services for development and manufacturing, consistent with the appropriate phase of drug development. Our method development philosophy is "fit for purpose," meaning we will provide the appropriate level of development/validation to support your API based on where your compound is in the development cycle.

Quality Assurance
The Quality Assurance (QA) team at CML ensures that every stage of the development and manufacturing process meets customer and regulatory expectations. Whether the product is going into the domestic or international market, CML will ensure that all compliance and quality standards are met.

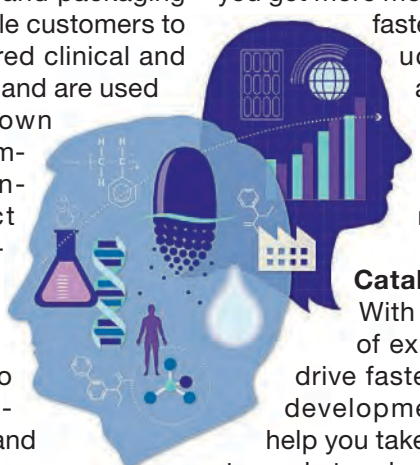
CAMBRIDGE MAJOR LABORATORIES INC.
CHEMISTRY THAT WORKS®

ADVERTORIAL

Catalent Pharma Solutions

www.catalent.com

Catalent Pharma Solutions is a leading provider of advanced dose for and packaging technologies as well as development, manufacturing, and packaging services for pharmaceutical, biotechnology, and consumer health companies. Catalent applies its local market expertise and technical creativity to advance treatments, change markets, and enhance patient outcomes. Catalent's proprietary drug delivery and packaging technologies enable customers to achieve their desired clinical and market outcomes, and are used in many well-known products. The Company provides innovative product development, superior quality, advanced manufacturing, and skilled technical service to support its customers' development and product needs.



Catalent holds more than 1,500 patents and patient applications in advanced drug delivery, biologics formulation, manufacturing, and packaging. With experience in more than 100 countries, extensive knowledge of the pharmaceutical, biotechnology, and consumer markets, and a global facility network that spans five continents, Catalent is well positioned to serve you, wherever you do business.

Description:

Catalyst + Talent
Our name combines these ideas. From drug and biologic development services to delivery technologies to supply solutions, we are the catalyst for your success. With over 75 years of experience, we have the deepest expertise, the broadest offerings, and the most innovative technologies to help you get more molecules to market faster, enhance product performance and provide superior, reliable manufacturing and packaging results.

Catalent develops
With our broad range of expert services we drive faster, more efficient development timelines to help you take more molecules to market and create more effective products.

Catalent delivers
As the world leader in drug delivery innovations, we have a proven record of enhancing bioavailability, solubility and permeability, improving ease and route of administration, and increasing patient compliance for better treatments.

Catalent supplies
Globally positioned to serve all your manufacturing and commercial packaging needs, we provide integrated solutions to take your product from design, to clinical trial, to plant, and to pharmacy.

Catalent. More products. Better treatments. Reliably supplied.™

Catalent®

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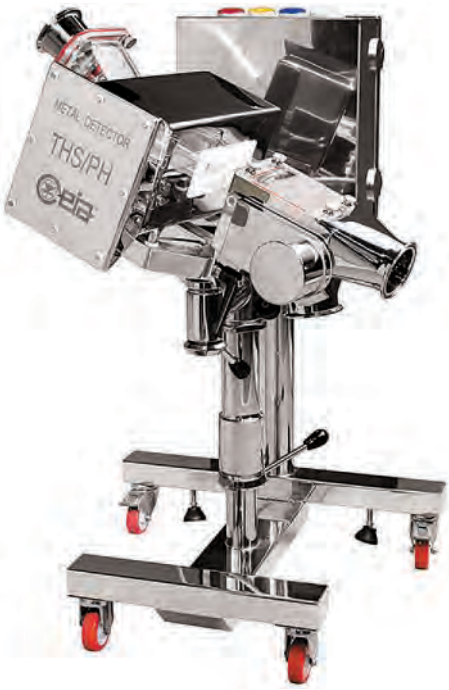
CEIA Pharmaceutical Metal Detection Systems

www.ceia-usa.com

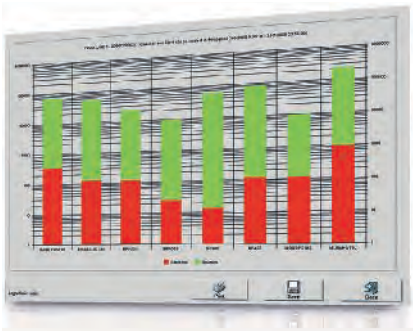


CEIA is a Market Leader that has been designing, engineering and manufacturing Metal Detectors for many industries worldwide for over 45 years. The core competence on electromagnetic fields affords the development for specific metal detection solutions in today's demanding industries.

The Pharmaceutical division includes several state-of-the-art Quality Control Metal Detectors that offer full compliance with FDA requirements Part 210 and Part 211. The THS/PH21N provides superior metal detection in the manufacturing process of this strictly regulated industry. The highly reliable proprietary digital technology delivers a consistent detection for metal contaminants in tablets, capsules and powders. All models feature a mirror finish on the 316L Stainless Steel that offers the best level of sanitation achievement.

Superior Detection Capability
CEIA THS/PH21N Metal Detection Systems feature extremely high detection sensitivity towards contaminating metals, whether ferrous, non-ferrous or stainless steel. Once a contamination is detected, the system rejects the identified material. The system's fail safe operation monitors the opening and closing of the ejection flap through a redundant confirmation sensor.

CEIA THS/PH21N Control Power Box available according to UL 508A and CSA-C22.2 No. 14-05.



Continuous embedded Self-Calibration
CEIA THS/PH21N introduces a continuous embedded Self-Calibration function for maximum repeatability and performance consistency over time. Proprietary signals are sent to the metal detector transmission and reception chain that provides constant monitoring of the detection characteristics. Constant regulation of algorithms supplies compensation for any variations caused by environmental factors. The result is system with stability, consistency in performance and effect product assurance.

FDA 21 Part 11 Compliant
CEIA THS/PH21N Metal Detection Systems satisfy the standards of Security, Integrity and Traceability of production data as required by Part 11 of Title 21 of the CFR – Electronic Records – Electronic Signatures.

CEIA USA Operations
CEIA USA supports the full line of Pharmaceutical Metal Detectors and the related services to clients in the United States, Canada and Puerto Rico.

Coating Place, Inc.

www.encap.com

Who We Are

Coating Place has developed and manufactured modified release solid oral dosage products for over 30 years. We are the leading provider of Wurster fluid bed microencapsulation services. CPI chemists have successfully developed a wide range of formulations and applied them to an equally wide range of core materials. Formulations are designed for a variety of desired outcomes including improved stability, shelf life, taste or odor masking, enteric delivery, controlled release, sustained release and delayed release. Our production staff includes numerous employees each with more than 20 years of coating experience. Every project is handled in a confidential manner and scheduled to meet your needs.

Honest and confidential research and manufacturing services have made us the leader and most trusted in the industry.

Suspension Technology

CPI introduces our new patent pending DRCs technology, an ion resin drug release system which allows us to create 12 hour time release liquid suspensions. These suspensions can be formulated to match the profiles of your current sustained release solid dosage forms to make filing less complicated. Good tasting easy to swallow liquids make it enjoyable to take your medicine. In our early history CPI created two products which featured ion resin suspensions. In over twenty years these products have not been duplicated. This technology is applicable to a wide range of APIs and can be filled into capsules or pressed into tablets.

Solid Dose Development

- Extrusion spheronization
- Chilsonation
- Development applications include controlled oral delivery such as enteric, delayed, sustained release, and taste masking.
- Analytical method development
- Stability studies (ICH conditions)

Solid Manufacturing Capabilities

- cGMP batch sizes from 10g to 600kg with multiple units
- Controlled substance capabilities Schedules II –V
- Solvent and aqueous formulations
- Capsule filling, tablet compression and coating

Facilities

185,000 ft^2 FDA registered facility is located in Verona, Wisconsin. Production suites are equipped with 15 different Wurster fluid bed coating units which produce batch sizes ranging from 0.010 to over 600kg. This year our coating capacity will reach 7 million kilograms. Coating Place Inc. continues to develop, manufacture, and operate proprietary cutting edge Wurster coating equipment. The possibilities are virtually limitless.

Coating Place Inc.
200 Paoli Street
Verona, WI 53593
Phone 608 845-5002

COATINGS™
Coating Place Inc.
THE ORIGINAL WURSTER TECHNOLOGY SOURCE

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Covance

www.covance.com/cmcpds

Covance is one of the world's largest and most comprehensive drug development services companies with more than 10,000 employees in 60 countries. Through its discovery, nonclinical, clinical, CMC development and commercialization services, Covance has helped pharmaceutical and biotech companies develop one-third of all prescription medicines in the market today. Covance has the people, processes, client service, and global resource capabilities to respond to the toughest drug development challenges.

Below is a brief introduction of Covance CMC development capabilities for small and large molecules. These offerings are fully GMP-compliant.

Small Molecule Chemistry, Manufacturing & Controls Development Services

Covance offers a comprehensive and integrated set of CMC Pharmaceutical Development Services, including **API development and supply, preformulation and formulation development, analytical and stability and regulatory documentation services**.

This offering is built on the perfect combination of top-five pharma expertise, experience and facilities, and decades of excellence client service record. Through this offering, Covance is committed to helping pharmaceutical companies reduce the time required to prepare IND or NDA submissions, improve the hit rate of molecules and increase the likelihood of application approval on the first pass.

Biotechnology Services: Large Molecule CMC Analytical and Testing Services

With over 250 different biomolecules successfully supported annually, we now offer you the most comprehensive biotechnology service in the industry.

Our experience covers a wide range of molecules, including recombinant proteins, monoclonal antibodies, vaccines, blood products, gene therapy products and more. Our capabilities include **protein analytical chemistry, immunocharacterization, cell banking, biosafety testing, viral clearance, bioassay studies, molecular biology, stability and release, biomanufacturing support** and more.

Customized and committed to clients large or small, Covance recognizes your development program is as unique as the product you bring to our facilities. You can choose to work with us on individual projects, milestone-based packages or full drug development solutions, whichever best fit the needs of your company and your molecule.

COVANCE®

Croda Inc

www.croda.com/healthcare

Corporate description

Croda Inc is a wholly owned subsidiary of Croda International Plc, a UK-based manufacturer and worldwide supplier of oleochemicals. As part of this global organization, Croda Inc offers one of the widest ranges of chemical specialties, surfactants, and high-purity lipids available to the pharmaceutical industry. Products are manufactured in the United States, the United Kingdom, Singapore, Japan, and Brazil. The Croda group provides international sourcing through a network of sister companies to supply products that are not manufactured locally.

Technical services

Croda produces a variety of excipients, including many that are compendial. To produce the diversity of products that the company offers, Croda uses several other technologies such as molecular distillation, esterification, ethoxylation, and fractionation. The focus of Croda's research is high-purity lipids, including a line of traditional excipients as well as a group of novel fatty acid concentrates. Croda products are used widely in topical and parenteral formulations and are finding expanded use in oral applications.

Major products

Croda offers a complete range of excipients for topical dosage forms as well as high-purity solvents, vehicles, and surfactants suitable for parenteral, oral, suppository and ophthalmic formulations. The company's products include:

- Super Refined®;
  - oils: including sesame, soybean, peanut, corn, olive, and cottonseed
  - oleic acid: high-purity multicompendial excipient
  - PEGs: high-purity, multicompendial polyethylene glycols
  - Polysorbates
  - dimethyl isosorbide: high-purity solvent for hydrophilic and lipophilic APIs, enhancing skin penetration
  - Etocas 35: high-purity polyoxyl 35 castor oil
- "Crodamols": a range of ester solvents and vehicles
- "Polawax": a complete compendial and self-emulsifying wax
- "Crodacols": fatty alcohols

- "Crodestas": sucrose esters for mild emulsification and sustainable release in tablet applications
- "Medilan": medical-grade lanolin designed to surpass USP requirements for lanolin, modified

CRODA
Health Care

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Dionex

part of Thermo Fisher Scientific

www.thermoscientific.com/dionex

Ultimate 3000 2x Dual LC

The Dionex UltiMate® 3000 x2 Dual Gradient Pump system is the ideal choice to maximize sample throughput for your conventional HPLC and UHPLC separations. The system combines the flexibility of ternary solvent selection with the productivity and performance of x2 Dual LC. Parallel and tandem configurations increase sample throughput by up to 100%, by automating two applications in one run. Multidimensional separations provide resolution impossible with single-column methods. On-line sample preparation saves time and reduces complexity, sample loss, and matrix interferences.

http://www.dionex.com/pt-ultimate3000-x2

Corona ultra RS Charged Aerosol Detector

The Dionex Corona® ultra™ RS is the newest of the Dionex range of Charged Aerosol Detectors (CAD®) with added features that enhance detection of non-volatile and some semivolatile analytes. The Corona ultra RS includes an on-board switching valve that allows the detector to be used independently of other detectors, without the need for system reconfiguration, and can divert unwanted components from samples. An optional variable ratio flow splitter makes it easier to use in parallel with MS without compromising resolution. A new data processing algorithm optimizes the data output for specific applications. All, making it easier to implement the Corona ultra RS detector with any (U)HPLC/HPLC system.

http://www.dionex.com/pt-corona-ultra

Chromeleon 7.1 Chromatography Data System

Dionex Chromeleon® 7.1 is the chromatography data system software that streamlines your path from samples to results. Whether your needs are simple or complex – whether your scope is a single instrument, a global enterprise, or anything in between. Unique new Interactive Charts instantly reveal patterns in results, and provide dynamic interactive links to chromatograms, spectra, and tables that invite exploration and discovery. Sequence set-up and processing, and result calculations can all be performed quickly, easily, and without training. It controls IC, LC and GC instruments from a wide range of manufacturers.

http://www.dionex.com/pt-chromeleon7

ADVERTORIAL

Dow Pharmaceutical Sciences

www.dowpharmsci.com

EXPERTS IN TOPICAL PRODUCT DEVELOPMENT

33+ years of topical product experience

By focusing exclusively on topical product development for over 33 years, Dow has developed more prescription topical formulations than any company in the world. We understand the problems that occur during development and know how to correct or prevent them. Dow has successfully developed topical formulations for hundreds of companies of all sizes. These formulations penetrate as required, are scalable and disease compatible. Of the 30 prescription topical dermatological product NDAs approved by the FDA in 2005-10, Dow developed the formulations for 11. By working with Dow you gain access to this expertise, and increase your chance of success.

Unique process for topical formulation development

Our formulation development and optimization process is unique. Experts in formulation, analytical, and drug transport collaborate to develop and optimize your formulation. Dow's *in vitro* skin penetration models are used to screen multiple prototypes for release and penetration. Results are used to optimize until a lead formulation and back-up are selected.

Rapid feasibility and proof of concept data for Go/No Go decisions on your molecule

For this you need penetration, stability, and clinical proof-of-concept (POC) data. We work with you to streamline the development plan to obtain POC data quickly. For this we use our *in vitro* penetration models, accelerated stability studies and, where appropriate, human POC models available at our bioskin® subsidiary.

Beyond product development–regulatory approval

We are experienced with regulatory planning and FDA submissions. Because we interact so frequently with the FDA Dermatology Division, we understand what it takes to get a product approved. Dow filed four NDAs in 2003-04; all four were approved in 2005-06. We develop non-clinical and clinical plans, and we file submissions electronically using ViewPoint® software.

Dow Pharmaceutical Sciences

The D in Topicals R&D

Since 1977

ADVERTORIAL

DPT Laboratories

www.dptlabs.com

About Us
DPT is the contract development and manufacturing organization (CDMO) that specializes in semi-solid, liquid and sterile dosage forms. With unmatched technical expertise and fully integrated drug development and manufacturing services for sterile and non-sterile dosage forms, we can help you successfully develop and commercialize your next product. Partnering with DPT gives you a seamless transition from pre-formulation to clinical supplies to commercial supply.

Semi-Solids & Liquids
Customers choose DPT as a strategic partner because of our ability to provide fully integrated drug development and manufacturing solutions. DPT customers have confidence that their projects, from concept to commercial manufacturing, will be handled by professionals with unparalleled knowledge and experience, using state-of-the-art equipment and processes.

The ability to develop, manufacture, and commercialize products in semi-solid and liquid dose forms makes DPT unique.

Research & Development
Whether your current development project is for pre-formulation of a new chemical entity or optimization of an existing drug delivery system, we can help. In addition, DPT can produce your clinical trial materials and assist with transferring clinical trial materials to your CRO. Our pharmaceutical development services can be a valuable resource to support your organization's development strategy.

Sterile & Specialty
Building on our reputation as the industry leader for semi-solids and liquids, DPT has recently invested over $30 million on the latest filling equipment and newest aseptic processing suites in the industry to efficiently manufacture your product. We provide unique solutions for clinical trial material manufacturing and a wide range of sterile commercial manufacturing options. Aseptic production of sterile dosage forms includes small-volume parenterals, ophthalmic preparations, preservative-free nasal sprays, sterile ointments, and specialty products.

DPT®

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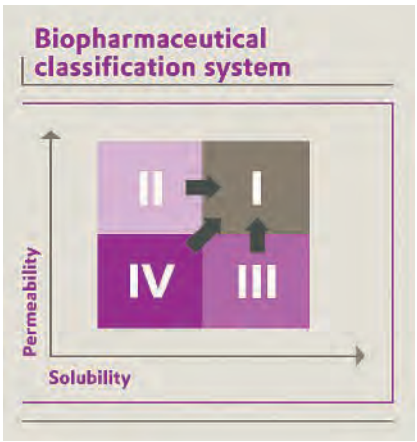
Evonik Pharma Polymers

www.evonik.com/eudragit



RESOMER® & EUDRAGIT® - Strong brands for the design of drug and device functionality.
Evonik Pharma Polymers, a business of Evonik Industries, is one of the world leaders in the manufacture and supply of functional coatings for the pharmaceutical industry. Through its EUDRAGIT® brand, Pharma Polymers has a leading position in the global market of pharmaceutical excipients. EUDRAGIT® acrylic polymers, the favorite choice for solid oral dosage forms, have become indispensable for enteric, sustained release and immediate release drug delivery formulations.

In March 2011, Evonik acquired the entire product portfolio of standard and customized RESOMER® polymers used in the manufacturing of medical devices and pharmaceutical formulations. Based on lactic and glycolic acids, RESOMER® polymers are fully biodegradable in the body. The lactic acid polymers are also used in the manufacturing of surgical screws, nails, and plates. The advantage is that these biodegradable devices disintegrate after a defined life span in the body without a negative impact, making further surgery to extract them unnecessary. Additionally, RESOMER® polymers make it possible to imbed active pharmaceutical ingredients, such as growth factors or antibiotics to support the healing process.

Evonik Pharma Polymers' services are adapted to meet the requirements of the pharmaceutical industry's value chain. We support our customers in their development process to bring products safely and quickly to the market. The development process chain consists of many single demanding steps, which are often accelerated when carried out in strategic partnership with specialists. Pharma Polymers provides global support for local custom-tailored drug delivery solutions. Our international network of technical service centers provides on-site support, with the same high-quality standard and flexible performance anywhere in the world. Together with our customers, we are steadily working on new therapeutic concepts and meeting drug delivery challenges.

EVONIK INDUSTRIES

ADVERTORIAL

Fette Compacting America, Inc.

www.fetteamerica.com

Fette Compacting's FE55: The Most Innovative Tablet Press Ever Built

New Machine Raises the Bar on Productivity, Flexibility and Availability

Fette Compacting, the leading supplier of tablet press equipment for pharmaceutical and nutritional applications, now offers the FE55, a tablet press that delivers unprecedented levels of productivity, flexibility and availability. Everything about the FE55 is innovative and industry-leading – including the fact that it is clad in easily-detachable, FDA-certified high-performance polymer panels and offers 360-degree access.

Highlights include:

- Unique filling system for simple, safe feeding
- Unrivaled ratio of punch stations to footprint leads to an increase in production output of up to 50 percent
- Ability to produce single- and double-layer tablets and direct pressing – the only machine of its compact size to offer all three capabilities
- Dust-tight, through-the-column discharge assembly for good, out-of-specification and sample tablets

New Compression Stations

The Fette FE55's newly developed compression stations provide maximum flexibility for mono-, double-layer and direct-compression tablet production. All totaled, the FE55 is equipped to handle approximately 90% of the most common tablet formats. Details:

- When configured for double-layer tablets, the device uses its optional third compression station as a tamping station for the first tablet layer
- The machine's double-layer tableting set-up features identical compression rollers and filling devices; direct compressing utilizes an easily installed / removed third compression station

Flexibility and Availability

- When configured for bi-layer manufacturing, the pneumatically-actuated lower roll assembly raises the first lower compression roll to temporarily increase the hardness of the first tablet layer. This allows the layer to withstand the trip through the sampling chute and be weighed
- Reverts to normal operation in just over four seconds
- Unique turret setup features smooth-running pressure rollers automatically driven into parking position for easy turret change
- Uncomplicated turret exchange with cams and segments, which allow for a fast format changeover

Ease of Operation

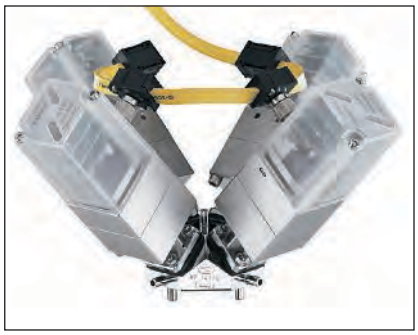
- The Fette FE55's Tri. Easy design allows for unprecedented ease of operation, changeover and maintenance
- The new Fette Compacting Human Machine Interface (HMI) offers intuitive operation for maximum efficiency and security, such as an enhanced visual operating platform, an SQL server database, and swift access to the machine's most important functions via 12 pictogram buttons

FETTE COMPACTING

ADVERTORIAL

GEMÜ Valves

www.gemu.com



GEMÜ offers the broadest range of Aseptic Diaphragm Valves and Multiport Valves compliant with FDA and USP regulations.

GEMÜ is renown for innovative design and latest manufacturing technology that result in custom multiport valves and unique automation components, providing engineered solutions to complex process challenges.

Automation options include Communication and Control Modules that facilitate commissioning and optimize diagnostic benefits of control network architecture.

Unprecedented precision, repeatability and reliability in communication and control are provided as a result of advanced sensor and microprocessor control technology.

Installation and operation economy, related to remote setting of switch points and remote addressing of network devices, is a benefit associated with GEMÜ Communication and Control Modules.

Recognition of space constraints inspired position feedback concepts that require less than half the envelope dimension of alternative brands.

Remote setting eliminates clearance requirements of alternate designs that require cover removal for local mechanical setting.

The **GEMÜ 651** unitized valve/actuator/pilot valve/position indicator, illustrated above, offers a unique solution in confined areas, particularly for fractional sized valves and small multiport configurations.

Testimonial to the performance, reliability and quality of Gemu and our products is evident by the inclusion of GEMÜ in design specifications worldwide and by recognition of GEMÜ as a global leader.

The **GEMÜ 1236** Position Indicator Features:

- Highly visible luminous indication
- Self setting
- Local or remote programming
- Continuous analogue sensing with microprocessor controlled setting offers enhanced repeatability and reliability
- Adjustable switch point settings
- No cover removal required
- Local and remote diagnostics
- IO-LINK communication enabled
- Compact profile for sizes ½”- 6”
- Optional AS-I interface
- Cable connection either M12 Euro-fast or 7/8” Minifast
- Enclosure rating: IP 67, NEMA 4, 4X
- Accuracy +/- 0.1 mm

GEMÜ® VALVES, MEASUREMENT AND CONTROL SYSTEMS

ADVERTORIAL

Grain Processing Corporation

www.grainprocessing.com

Grain Processing Corporation (GPC) is dedicated to serving the pharmaceutical industry with multiple lines of specialty excipients providing a wide range of functionality. GPC continually expands its line of specialty ingredients to meet the changing requirements of customers worldwide.

MALTRIN® Maltodextrins and Corn Syrup Solids NF are excellent binders and diluents for direct compression tablets, granulations, powder blends and capsules. They are versatile excipients for bulking and carrying and provide a smooth mouthfeel for chewable applications.

MALTRIN QD® Maltodextrins NF offer exceptional dispersibility, flow and bulking properties. They function as direct compression binders and diluents and can carry oils and other ingredients into powder blends, tablets and capsules.

Spress® Pregelatinized Corn Starches NF are white, free-flowing starches designed for binding, bulking, lubricating and disintegrating properties. The starches in the Spress® family range in pregelatinization so the optimal product can be chosen for the desired application. Wet granulation, direct compression, moisture activated dry granulation and capsules are just some of the application areas for which Spress® starches are ideal.

PURE-COTE® Modified Starches NF and INSTANT PURE-COTE® Pregelatinized Modified Starches NF generate clear, soluble films for coatings, oral thin films, softgel capsules and granulations. They have excellent sheen and solubility and are production friendly. They can replace gums, gelatin and hypromellose.

PURE-DENT® Corn Starches NF and USP range from basic unmodified starch to very specialized, innovative starches for unique applications. They are used in direct compression tablets, granulations, dry blends and topical applications.

PURE-DENT® Absorbable Dusting Powders USP are lubricating powders to aid in donning products such as examination gloves, condoms, etc. GPC is an FDA-approved producer of USP-grade absorbable dusting powder for use in surgical gloves.

GPC produces natural ethyl alcohol for a variety of products, including specialty denatured alcohols, specialty solvents, duplicating fluids and other applications.

TruBran® corn bran contains a minimum of 75 percent total dietary fiber and is an excellent source of fiber for tablets, capsules, granulations, beverages, nutritional bars and other fiber-fortified formulations.

GPC™

Exceptional Products
Unparalleled Service

ADVERTORIAL

Hospira One 2 One

www.one2onecmo.com

Who We Are

Hospira is a global specialty pharmaceutical and medication delivery company dedicated to developing, manufacturing and marketing products that help improve the productivity, safety and efficacy of patient care. The company's One 2 One® contract manufacturing business is a world leader in the custom development and manufacture of parenteral products packaged in vials, prefilled syringes, cartridges, flexible containers and ampuls. One 2 One offers parenteral development and manufacturing services at its nine worldwide facilities. Whether your product is a small molecule or advanced biologic, One 2 One's highly qualified personnel in every world-class facility ensure quality, capacity and security of supply.

Drug Delivery and Prefilled Syringes

One 2 One® provides a wide variety of drug delivery options. It's about developing simple solutions to streamline workflow, improve accuracy, and decrease waste and costs. One 2 One meets your unique product needs for a distinct advantage in the marketplace. With One 2 One, you have access to broad prefilled syringe filling capabilities. Whether your product is administered via IV, IM or subcutaneously, or you need a unique diluent for your lyophilized product, One 2 One is your comfort zone for contract manufacturing and prefilled syringes.

iSecure™ Cartridge Syringe

As a prefilled, disposable syringe, the proprietary design of Secure™ delivers efficiency and simplicity to ensure accuracy and lower costs.

Glass Prefilled Syringes

Prefilled syringes are available in luer and staked-in needle configurations, and our packaging line is compatible with the UltraSafe Passive® Needle Guard offered by Safety Syringes Inc.

Glass Cartridges

Prefilled cartridges are available in 1 to 3 mL sizes, and are compatible with industry leading auto and self-injector devices.

Ansyr® Syringe

Emergency medications and custom diluents can easily be delivered in this one-piece, polypropylene plastic, prefilled syringe.

ONE 2 ONE®

A Service of Hospira

ADVERTORIAL

Jubilant HollisterStier,

Contract Manufacturing & Services Division

jublHS.com

Jubilant HollisterStier is a global manufacturing service provider, able to aseptically fill liquid, lyophilized, semi-solid, and solid dosage forms in our facilities across North America and India. Jubilant HollisterStier represents the CMOs formally branded as HollisterStier Contract Manufacturing and Draxis Pharma, as well as non-branded solid dosage sites in Maryland and India. New branded name and logo, same quality service.

Quality is part of Jubilant HollisterStier's corporate culture and is held to a high standard throughout our facilities. We provide a full-range of support and services to streamline the manufacturing process such as on-site assistance from process qualifications and regulatory submittals through product release. Jubilant HollisterStier's Quality Unit maintains an integrated quality assurance program that emphasizes quality design, validation, and proper use of facilities and equipment.

Jubilant HollisterStier manufactures the following dosage forms in the locations noted:

Sterile Fill/Finish—*Spokane, WA*
- Phase I-commercial sterile injectables, lyophilization

Sterile and Nonsterile Fill/Finish—*Montreal, Quebec, Canada*
- Commercial sterile injectables, lyophilization, and opthalmics
- Nonsteriles, topical creams/ointments, and liquids

Small-Volume Commercial Solid Dosage—*Salisbury, MD*
- Tablets and capsules

Large-Volume Solid Dosage—*Roorkee, India*
- Tablets and capsules

Certified Project Managers work with our clients and our expert staff throughout the manufacturing process to ensure that projects are processed efficiently and safely. We are committed to providing exceptional quality, regulatory expertise, and operational excellence to ensure streamlined processes and services in all facilities.

For more information about Jubilant HollisterStier, please visit *jublHS.com*.

JUBILANT HOLLISTERSTIER
CONTRACT MANUFACTURING & SERVICES

ADVERTORIAL

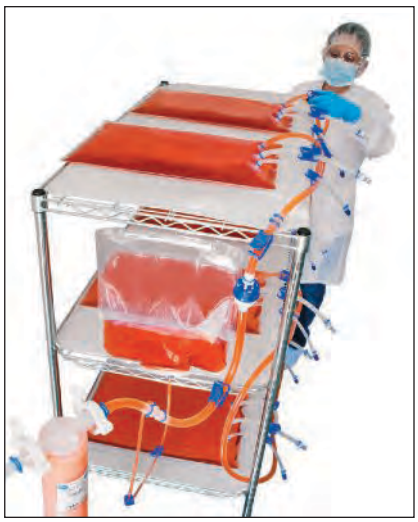
Meissner Filtration Products

www.meissner.com

Meissner is your source for innovative microfiltration and single-use systems. We are a technology centric company that leverages our R&D efforts to offer our clients products that deliver advanced processing and fluid handling solutions for the pharmaceutical and biopharmaceutical industries.

Our One-Touch® single-use product portfolio demonstrates our commitment to manufacture innovative products for use in today's biopharmaceutical manufacturing operations.

TepoFlex® PE-based biocontainers were designed to deliver the highest levels of fluid integrity provided by any existing product in industry. By engineering slip agents out of the TepoFlex® film and biocontainer manufacturing process, we



substantially reduced the film's overall extractables profile, while also imparting remarkable visual clarity to the biocontainer. Providing the industry's highest combined gas and water vapor barrier, TepoFlex® biocontainers mitigate the risk of product degradation due to gas exchange and concentration loss due to water vapor egress. TepoFlex® biocontainers are designed to be durable and impact resistant with over 95% of the film's strength retained in the seams where there is the greatest potential for a breach of fluid integrity.

The introduction of FluoroFlex®, the industry's only multilayer PVDF biocontainer, demonstrates our commitment to providing cutting edge solutions that otherwise would not exist in the marketplace. FluoroFlex® biocontainers were developed for applications that are prone to nonspecific lipid and protein adsorption. FluoroFlex® film is extremely durable, yet flexible, and provides very high gas- and vapor-barrier properties. The inherently pure PVDF product contact layer contains no additives and gives FluoroFlex® biocontainers the lowest extractables profile of any biocontainer available today.

Meissner's TepoFlex® and FluoroFlex® biocontainer assembly portfolios are supported by extensive Qualification Guides. These guides provide all the technical and quality documentation necessary to facilitate your validation process. Meissner's technical expertise in designing single-use systems from development through production scale gives our clients a significant advantage. We specialize in catering to each client's process and whether the system is a simple buffer hold assembly, or a multi-assembly bulk product storage to final fill and finish configuration, our design experts will provide optimized process flow recommendations and validation support.

MEISSNER
FILTRATION PRODUCTS, INC.

ADVERTORIAL

Metrics, Inc.

www.metricsinc.com

METRICS INC.'S POTENT FACILITY PROVIDES TOTAL ENGINEERED CONTAINMENT

Metrics Inc.'s state-of-the-art potent and cytotoxic drug development facility provides total engineered containment of pharmaceutical processes through customized hard-wall isolation technologies.

With these technologies, Metrics has eliminated any need for powered air purifying respirators (PAPRs). Equipment and change parts are dedicated exclusively to potent and cytotoxic use, and containment is achieved at levels approximately 30 nanograms per cubic meter of room air.

All of which makes Metrics' dedicated facility unique for a CDMO.

The facility features two processing rooms with independent entry double airlocks, independent decontamination showers and exit airlocks, independent equipment airlocks, and access to a dedicated washroom. It is designed for one-way flow of material, personnel and equipment.

A dedicated air handler brings in 100% outside air with HEPA-in and HEPA-out filtering at the rate of 11,000-ft^3 per minute and 25 air changes per hour. There are pass throughs for the export of product and waste as well as dedicated equipment storage.

These facility features allow Metrics to handle materials with an OEL down to 30 nanograms per cubic meter of room air. After every campaign, Metrics conducts comprehensive health-based cleaning verification of shared surface areas. The isolated equipment permanently housed inside the potent facility includes:

- Fluid Energy Jet-O-Mizer micronizer
- Fitzpatrick Fitz L1A
- Globe Pharma Mexi-Blend (0.5 to 16 quart)
- Vector TFC Lab micro roller compactor
- Fluid Air Pharm X high shear granulator with 1L, 2L, 4L and 8L bowls
- Vector FLM1 fluid bed dryer/top-spray granulator
- Quardro Comil U-5 model
- Riva 10-station instrumented Picolla tablet press
- Capsule filling devices
- Tablet film coater

Headquartered in Greenville, North Carolina, Metrics Inc. is a full-service provider of quality pharmaceutical formulation development; first-time-in-man (FTIM) formulations; clinical material manufacturing (CTM) for Phase I, II and III trials; commercial manufacturing; and analytical method development and validation services. To learn more, visit *http://www.metricsinc.com*.

ADVERTORIAL

Mettler Toldeo

www.mt.com/TA-FlashDSC

Figure 1

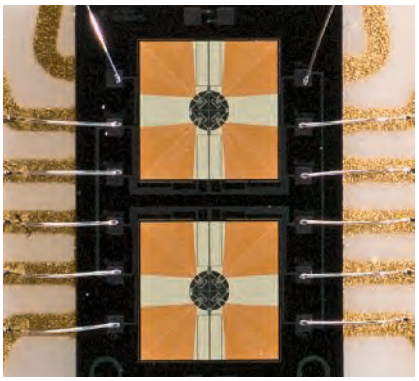


Figure 2

The Worldwide Technology Leader in Thermal Analysis

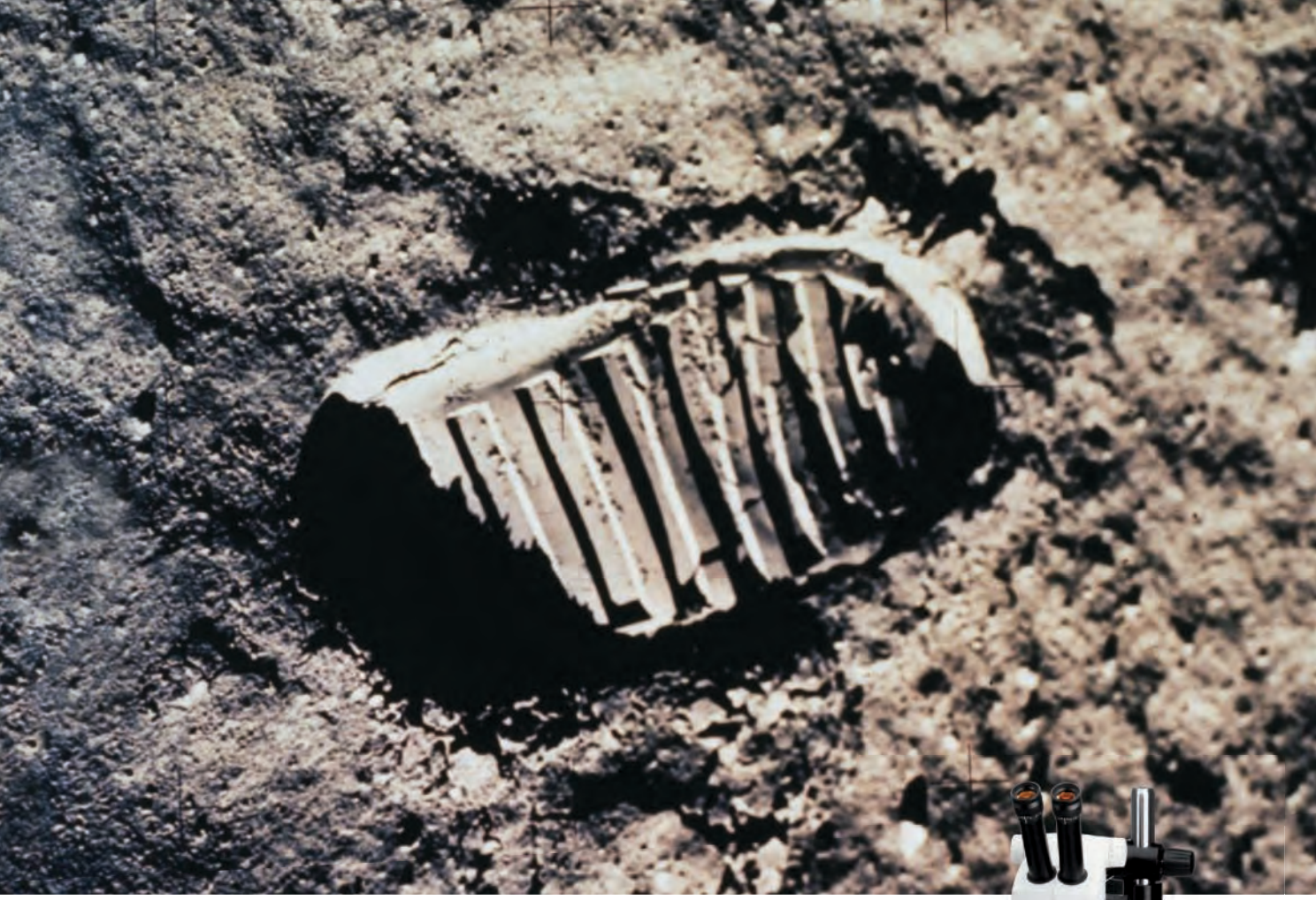
The commercialization of the DSC (Differential Scanning Calorimetry) technique in the 1960s led to a rapid expansion of this method for the thermal characterization of materials. The great strength of DSC is that complex information can be quickly obtained about physical transitions, the structure of materials as well as the kinetics and composition of chemical reactions.

Conventional DSC instruments perform measurements at heating rates of up to 500 K/min and cooling rates of 200 K/min with a signal time constant of about 1 to 2 seconds. This is not adequate for the investigation of the structure and morphology of polymers and polymorphic substances or of meta-stable materials in general. Different cooling rates can lead to changes in the meta-stable structure when materials are cooled from the melt. This specific reorganization often cannot be measured in the DSC because the result curve consists of exothermic and endothermic events that take place simultaneously. A new technology is needed to further investigate these systems, suppress decomposition and detect all possible polymorphic structures.

The Flash DSC 1 (Fig. 1) is a completely new type of commercial DSC with a signal time constant of less than 1 millisecond. This allows very high heating and cooling rates to be achieved in the range is 1 K/s to 40,000 K/s (60 K/min to 2,400,000 K/min). The heating rate overlap with conventional DSC is complimentary and offers over six decades of heating rate for experimentation. The UFS 1 MultiSTAR sensor is based on MEMS technology (MEMS: Micro-Electro-Mechanical Systems) and is made up of two separate calorimeters on a removable sensor chip (Fig. 2). It consists of two identical quadratic silicon nitride membranes with a thickness of 2 µm. The sample area has a diameter of 0.5 mm and is coated with aluminium so that a homogeneous temperature profile is obtained. The temperature of this area is measured by means of eight thermocouples and resistive heaters are used to heat very quickly. Samples can be prepared and cycled many times to understand the effect of high heating and cooling rates, stored for archiving purposes and re-investigated again at a later date. Organic materials typically have a mass between 10 ng and 10 µg and the mounted stereo microscope aids sample preparation and placement.

The Flash DSC 1 opens the door to the wider experimental parameters required to investigate the meta-stable and time-dependent transitions of materials. Very fast cooling and heating rates allow researchers to generate material under real process conditions (cooling) and then measure those material properties (heating) to gain a never before seen perspective into their materials.

METTLER TOLEDO



It's Really More of a Giant Leap...
The New Flash DSC 1

The Flash DSC 1 represents a giant leap in Thermal Analysis technology and revolutionizes fast-scanning Differential Scanning Calorimetry (DSC). Its incredibly high heating and cooling rates enable exploration of exciting new applications under exactly the same conditions that occur in your existing process.

An ideal compliment to the conventional DSC, the Flash DSC 1 heats samples so quickly that recrystallization and reorganization processes can be supressed and studied — like walking on the moon, it was once thought impossible.

For 50 years, we have been committed to providing technlogy leading solutions and striving to expand the boundaries of instrumentation.

It's what you should expect from The Technology Leader in Thermal Analysis.

Heating rates up to 2,400,000 °C/min (40,000 °C/sec)
Cooling rates up to 240,000 °C/min (4,000 °C/sec)

www.mt.com/us-giantleap

Experience the Flash DSC 1 in action!

METTLER TOLEDO

2011 R&D 100

2011 Winner of the
R&D 100 Award

ADVERTORIAL

MG America

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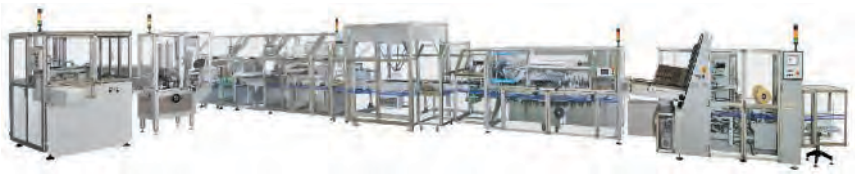


DESCRIPTION

MG America, a subsidiary of MG 2 (Bologna, Italy), is a recognized leader in the supply of processing, packaging, assembly and inspection machinery to pharmaceutical manufacturers throughout the United States, Canada, and Puerto Rico.

FACILITIES

MG America operates from a 20,000-ft^2 facility located in Fairfield, NJ where our in-house staff provides complete services including sales, field service, spare parts, and machine trials.

PRODUCTS AND SERVICES

MG2 Packaging/Assembly Machinery:

Through MG2's Packaging Division, MG America offers packaging equipment designed for flexibility, compact operation, ease of use and maximum reliability including: Casepackers, pouching machines, cartoners, thermoforming machines, blister packaging machines, palletizers, tray formers, tube fillers, mixing machines, syringe assembly equipment, inspection systems and aseptic filling machinery.

The LABBY Capsule Filler

The LABBY is a modular, compact capsule filler that is fully automatic and can operate in either continuous or intermittent mode. The LABBY can fill up to 3,500 capsules per hour and is designed to handle all kinds of powder. The unit is complete with a 100% microweighing control system of the net product weight and control system accuracy of ± 0.1 mg of the net weight. Its small footprint makes it the perfect choice for R&D laboratories, clinical trials, small batch outputs and special productions.

MG2's Additional Capsule Filling Machinery:

Aside from the LABBY, MG America offers a complete selection of capsule fillers designed to satisfy even the most challenging capsule filling needs. Capsule filler speeds range from 6,000 to 200,000 capsules per hour. Dosage forms that can be filled include powders, pellets (beads), tablets, and liquids. Capsules can be filled either as a single dose, multiple dose, or in combination with other dosage forms. The company also offers several innovative weight control systems.

MG AMERICA IS YOUR SINGLE SOURCE SOLUTION FOR PREFILLED SYRINGES

MG America is proud to offer a complete line of innovative equipment for the manufacture of prefilled syringes. Capabilities include filling, inspection, assembly, labeling, and packaging.

MG AMERICA
A partnership for success

ADVERTORIAL

MPI Research

www.mpiresearch.com

MPI RESEARCH –
Your Responsive CRO

MPI Research, with global headquarters in Mattawan, Michigan, provides discovery, safety evaluation, bioanalytical, and analytical services to the biopharmaceutical, medical device, animal health, and chemical industries. Responsiveness, scientific knowledge, and experience, integrity, trust, teamwork, and dedication to strong and enduring Sponsor relationships are the defining attributes that characterize MPI Research as a high-performance, high-quality organization.

Our open and responsive culture is evident in the collegial, collaborative atmosphere at MPI Research. Sponsors find communication with their counterparts within the company to be refreshingly easy, frequent, and informative. Study Directors are uniquely accessible on a real-time basis and proactive in keeping you informed as developments unfold, from collaboration on the initial program design through final report.

A Full Spectrum
of Integrated Services

MPI Research has conducted thousands of drug safety, discovery, and bioanalytical and analytical studies. The company's internal structure allows us to respond and adapt rapidly, from making last minute scheduling changes to developing new capabilities as needed. We test a wide and diverse range of compound classes, provide all routes of administration with the exception of inhalation, and offer studies with numerous species and models. With ample physical and technical capacity, we can accommodate multiple requirements simultaneously, adjust schedules readily, and produce results quickly.

Biologic Expertise

MPI Research built its reputation on its toxicological experience and knowledge with small molecules. However, the company is ahead of the curve in responding to recent market trends with biopharmaceuticals. Our scientific experts understand the many significant ways in which the development process of a large molecule differs from that of traditional small molecules, including immune response, dose solution preparatory considerations, species-specific pharmacologic factors, and delivery methods. MPI Research has the experience and knowledge to meet all of your development needs for both large and small molecules.

MPI RESEARCH Customized. Responsive. On-Time.™

ADVERTORIAL

Natoli Engineering Company, Inc.

www.natoli.com

Applying accurate and consistent compression force with a manual laboratory tablet press can be quite difficult and sometimes dangerous. Inaccurate compression force can cause inconsistencies among tablet density and thickness, ultimately leading to variable friability and dissolution. In order to combat this problem, Natoli has developed the NP-RD10A tablet press.

The NP-RD10A is a single station, benchtop tablet press ideal for pharmaceutical laboratory research and development when only small samples are available for testing. Using this press eliminates the handling of multiple tool parts to compress a single tablet, and when used in laboratory research, significantly helps to maintain tablet uniformity, reduce trial and error, and improve production efficiency.

The NP-RD10A is CE-certified and constructed with unique features such as multi-layering capabilities; micro-adjustable depth of fill provides extremely accurate layer weight control; digital depth of fill gauge that optimizes tablet weight consistency; digital process meter for compression and ejection force display; programmable parameters for compression force control and automatic cycle return; quick tablet ejector lever easily ejects tablet, eliminating the need for disassembly; extra deep fill capacity; a 10 U.S. ton/10 Metric ton capacity; RS 485 serial communications output; ½" thick Lexan® guards, which serve as safety shields; electro-less nickel coated steel construction; and utilizes "TSM" or "EU" "B", "D" and "F" standard tool configurations.

Established in 1973, Natoli is the world's premier manufacturer and supplier of tablet compression tooling, presses, replacement parts, accessories, software, services, and training. Dedication to excellence, steadfast determination, innovative thinking, and a commitment to providing extraordinary customer service have propelled Natoli to the forefront of the tablet compression industry.

NATOLI

ADVERTORIAL

Pall Life Sciences

www.pall.com/allegro

Validated Allegro™ Single-use Technology at Multiple Scales

Pall Allegro single-use systems can be used at all scales, from development to full production scale and for applications from upstream to final formulation and filling. With consistent materials of construction, single-use systems are ideal for scaling up or scaling down your process, and now incorporate technologies such as biocontainers, sterile connectors/disconnectors, mixers, sterile/virus filtration, chromatography and tangential flow filtration.

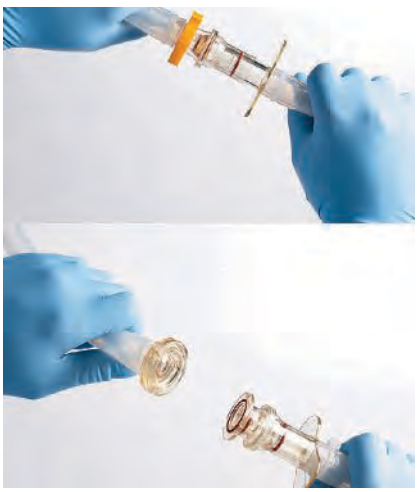
Systems are provided as integrated validated solutions to meet regulatory and industry recommendations. With minimal operator interaction, enhanced safety and robustness, and high product recoveries, the unique design of Pall Allegro systems means single-use technology has never been so easy and reliable to use.

Integrated Technologies: Kleenpak™ Sterile Connectors and Disconnectors

The easy-to-use Kleenpak sterile connector allows for the dry connection of two separate sterile fluid pathways, while maintaining the sterile integrity of both. Available in multiple sizes for maximum flexibility.

The Kleenpak sterile disconnector provides an easy-to-use and secure method for the permanent sterile disconnection of fluid pathways; maintaining sterility of the fluid path before and after disconnection.

Rigorously validated under worst-case conditions, you can be sure these connections/disconnections remain sterile every time...even in non-controlled environments.



Allegro Single-Use Systems

Allegro biocontainers are designed for maximum flexibility and high product recovery. The entire bio-container range (volumes 50mL-1500L) is manufactured with the same very high quality transparent LDPE film, enabling systems to be easily scaled-up without film requalification.

Allegro Single-Use Mixers

Combining critical requirements for single-use technologies, such as extreme ease-of-use, with established criteria for sound engineering principles for mixer design, Allegro mixers deliver the ultimate in mixing performance in critical applications, combined with the processing benefits of single-use. Utilizing the same film as standard Allegro biocontainers, Pall provides consistent materials of construction for systems used in any bioprocessing application.

Visit www.pall.com/allegro or email allegro@pall.com

PALL Life Sciences

Restek Corporation

www.restek.com/pharma

Company Description
Innovative products and exceptional customer service make Restek the chromatography supplies company of choice for the pharmaceutical industry. Our product lines include general and specialty liquid and gas chromatography columns, instrument parts and accessories, sample preparation products, and analytical reference materials. We specialize in innovative and dependable stationary phases for LC and GC columns and offer the widest range of selectivities in the industry—many of which outperform more conventional phases. At Restek, we stay on the forefront of new product development through our commitment to ground-breaking chemistry, stringent quality standards, and expert technical support.

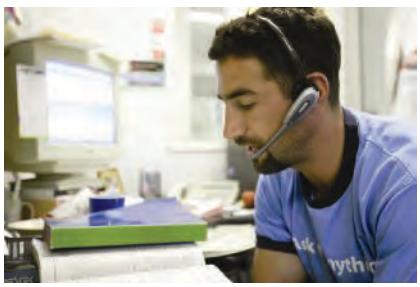
Chief Chromatographic Techniques Supported
UHPLC
HPLC
LC/MS
GC
GC/MS

Major Products and Services
Restek's commitment to continuous innovation sets us apart from our competitors. We introduce and stock hundreds of new products every year—designed by chromatographers for chromatographers.

Key products include:

- Exceptional columns for UHPLC, HPLC, LC/MS, GC, & GC/MS.
- Innovative accessories, instrument replacement parts, & consumables.
- Sample prep supplies.
- Stock and custom-prepared analytical standards.

Outstanding quality defines not just our products, but also our service. We focus on getting you what you need, when you need it. Our Customer Service Team will suggest time- and money-saving options and is dedicated to getting your products to you fast. Our Technical Service chemists can help you from analytical set-up to new method development. Visit our website and review an extensive



archive of technical publications, chromatograms, step-by-step guides, interactive calculators, animations, and training opportunities, all backed by a technical team dedicated to resolving your analytical challenges.

At Restek, we are dedicated to supporting pharmaceutical development. How can we help you today?

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Bellefonte, PA 16823

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p: 800-356-1688
f: 814-353-1309
e: support@restek.com

RESTEK

New Packaging Option for Products Sensitive to Humidity and Temperature

When Ropack began production in a $9 million state-of-the-industry dedicated manufacturing facility in May, trend-setting packaging solutions became available to global pharmaceutical and consumer health-care companies which have humidity- and temperature-sensitive products.

The 15,000-square-foot facility provides uni-dose packaging of solid oral dosage in Class 100000 clean rooms, each ensuring low relative humidity (20%), controlled temperature and controlled residual oxygen (<4%). The new production suite is part of the contract manufacturing and packaging company's 210,000 square feet of manufacturing, packaging, warehouse and distribution space. The facility, currently handling stickpack production, reflects Ropack's commitment to being an industry-leading force.

In addition to the latest technology and equipment, the Ropack team has considered every detail to ensure product integrity. Mechanical rooms are positioned to prevent interference from outside contaminants. Flow of product and personnel assures cleanliness and efficiency. Strict procedures and documentation are followed to maintain the highest standards.

"We have taken every step to ensure that our new dedicated suite far exceeds what is available elsewhere in North America to our clients," states Yves Massicotte, Ropack's President and CEO.

Ropack is particularly enthusiastic about introducing stickpack into its broad range of packaging services and is taking a primary role in advancing stickpacks in the North American market. A preferred packaging format in Europe and Asia since the 1970s, these slim, sealed, tube-shaped packets – approximately the size of a stick of gum – hold significant opportunity for the pharmaceutical and consumer health-care industries.

Beyond being an innovative design, stickpack offers product safety, reduction in cost, marketability and consumer convenience. "I believe that our new facility provides the pharmaceutical and consumer health-care industries the highest level of quality and efficiency in stickpack packaging," notes Paul Dupont, Director of Business Development.

In addition to stickpack, Ropack is equipped to perform standard and cold-form blistering, encapsulation, bottling, sachet filling, syringe assembly, clinical trials and blending.

The launch of the facility occurs during Ropack's 35th anniversary.

Ropack is a contract manufacturing and packaging solution provider for the pharmaceutical and consumer health-care industries, suffering primary and secondary pharmaceutical packaging services. Ropack operates ambient and refrigerated warehousing space, providing temperature-monitored distribution services to wholesales, representatives, physicians and clinical study sites in Canada and the U.S. Facilities are cGMP compliant, site licensed by the FDA and Health Canada certified.

ROPACK®

Uniquely Positioned to Manufacture and Package Probiotics.

Contact Paul Dupont for more details:
paul.dupont@ropack.com
513.846.0921

1-888-353-7090
www.ropack.com

ADVERTORIAL

ROQUETTE

www.roquettepharma.com

ROQUETTE *is a global manufacturer of pharmaceutical excipients and actives. As a leading global partner of the pharmaceutical industry, ROQUETTE has been actively developing starch-based functional pharmaceutical excipients active ingredients and nutraceutical ingredients to enable outstanding formulations. The US FDA and European authorities regularly audit our manufacturing facilities guaranteeing consistent compliance and reliability of ROQUETTE's services and products to the highest international quality requirements.*

LEADING ROLE IN INJECTABLES AND DIALYSIS SOLUTIONS

ROQUETTE is the specialist of excipients for injectables and dialysis solutions. Produced for over 20 years, pyrogen free dextrose monohydrate LYCADEX® PF is used by majority of pharmaceutical companies involved in the production of injectable solutions and infusions.

The established range also includes pyrogen free polyols (PEARLITOL® PF mannitol, and NEOSORB® PF sorbitol) and **KLEPTOSE**®HPB, pyrogen free hydroxypropyl beta-cyclodextrin. Committed to providing the most complete range of safe and reliable products for dialysis and parenteral applications, **ROQUETTE** most recently introduced pharma grade **LACTATE** and **GLUCONATE** salts.

THE POLYOL WORLD LEADER

Thanks to its leadership in polyols, ROQUETTE offers the broadest polyol excipient range providing excellent chemical stability with good taste, sugar-free sweetness and oral health benefits for numerous pharmaceutical applications.

This includes:
PEARLITOL® crystalline mannitol and granulated mannitol,
NEOSORB® sorbitol,
SweetPear™ maltitol,
XYLISORB® xylitol and
LYCASIN® maltitol syrups

FUNCTIONAL EXCIPIENTS FOR FORMULATION CHALLENGES

A dedicated manufacturing, research and QC network in Europe, Asia, and USA enables ROQUETTE to develop functional excipients such as DILUENT-BINDERS, GRANULATION BINDERS, DISINTEGRANTS and FILM COATING POLYMERS.

An in-house team of scientists is able to contribute to the design of pharmaceutical formulations and facilitate customers' developments, notably in the areas of:

- Tablets obtained by direct compression or wet granulation
- OTC and nutraceuticals as fiber sources and mineral supplements
- Syrups, suspensions, Granules and sachets
- Tablet Film coating and Thin-film delivery systems
- Toothpastes and mouthwashes
- Injectables (enteral and parenteral solutions)

FOCUS ON INNOVATION

The demand for novel functional excipients and health supplements continues to grow steadily. Thanks to our longstanding track record in excipients and actives innovation, ROQUETTE is ready to meet this challenge:

NUTRIOSE® soluble fibers for nutraceutical formulations and clinical enteral nutrition
NUTRALYS® – a new natural, nonGMO, allergen free pea protein
LYCOAT® Novel starch-based polymers specifically developed for fast and simple aqueous film coating
LYCATAB® **Mineral** – a compound developed for mineral supplementation for nutraceutical and OTC applications
PEARLITOL® mannitol as outstanding diluent-binder for solid dosage forms
KLEPTOSE® cyclodextrins for molecular encapsulation/ solubilization

ROQUETTE

Facing problems with solubility or stability ?

KLEPTOSE® HPB

KLEPTOSE® HPB and HP comprise a range of accessible hydroxypropyl cyclodextrins used increasingly as formulation aids to solve difficulties with aqueous solubility, stability or taste. KLEPTOSE® HPB and HP are available as compliant cGMP grades that are particularly useful for parenteral solutions, syrups and oral suspensions, as well as for dry formulations.

We deliver!

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ROQUETTE

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Sartorius Stedim North America Inc.

www.sartorius-stedim.com

SARTORIUS STEDIM BIOTECH is a leading provider of cutting-edge equipment and services for the development, quality assurance and production processes of the biopharmaceutical industry. Its integrated solutions covering fermentation, filtration, purification, fluid management and lab technologies are supporting the biopharmaceutical industry around the world to develop and produce drugs safely, timely and economically. For next generation processes, Sartorius Stedim Biotech focuses on single-use technologies and added-value services to meet the rapidly changing technology requirements of the industry it serves. Strongly rooted in the scientific community and closely allied with customers and technology partners, the company is dedicated to its philosophy of "turning science into solutions".

Sartorius Stedim Biotech, headquartered in Goettingen, Germany and Aubagne, France, is an international market and technology leader in biotechnology. With manufacturing and sales companies in North America, Puerto Rico, Europe and Asia, Sartorius Stedim Biotech maintains a worldwide presence.

Filtration: A complete, scalable array of filter capsules and cartridges for all bioprocessing steps –backed by decades of experience in filter technologies.

Fermentation: The widest range of bioreactors and fermentors from benchtop to process scale and from disposable to reusable technologies.

Fluid Management: Pioneer and leader in single-use systems, freeze-thaw processing and aseptic transfer systems, with the most extensive capabilities for creating fully integrated, single-use biomanufacturing solutions.

Laboratory: Advanced and scalable cell culturing, filtration and purification technologies as well as microbiological analysis and lab water systems.

Purification: A leading position in crossflow filtration, membrane chromatography and virus removal technologies for state-of-the-art initial recovery and contaminant clearance in biomanufacturing.

Services: Expert services for process optimization, validation and regulatory support – rapidly deployable and globally.

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ADVERTORIAL

Sheffield Bio-Science

A Kerry Group Business

www.SheffieldBioScience.com

A leader in innovation and applications of excipients

For more than 65 years, Sheffield has earned its reputation for reliability and excellence in serving the biotech, pharmaceutical and nutrition markets by delivering unsurpassed product value, enhanced opportunities for supply chain consolidation, and new technology innovation.

As a Kerry Group Business, customers benefit from our application expertise and vast global resources of a $6 billion global leader. We have the worldwide resources and global technical platform to deliver consistent, high quality products backed by unparalleled service, technical support and formulation customization capabilities.

Our technologies are manufactured in CFR 210-211 registered and/or FDA inspected facilities, manufacturing under IPEC Guidelines for cGMP compliance as well as regional requirements globally.

The Standard of Comparison

We deliver the industry's most extensive lactose product line in the industry, including anhydrous, spray dried, monohydrate, and inhalation lactose grades. We provide a variety of standard particle sizes to meet formulation needs and have the technical capabilities to develop customized characteristics for any formulation.

Sheffield Bio-Science's Innovative Technologies

SheffCoat™ Coating Systems are one step, ready-to-use film coating systems offering a full spectrum of best-in-class, cost effective solutions for specific functional requirements. They are based on industry standard, regulatory accepted polymers, pigments and plasticizers that are applied with standard film coating processes and equipment. SheffCoat™ matches or exceeds the functionality of any competitive coating system and can be customized to match any desired color.

LubriTose™ is a co-processed, highly functional excipient (HFE) that revolutionizes direct-compression, high-speed tabletting operations by eliminating blending issues associated with lubricants such as magnesium stearate. It is a complete formulation available in anhydrous, spray dried and microcrystalline cellulose versions that enhances tabletting capabilities and effeciency. LubriTose™ solutions save time and money, allowing larger batch sizes at faster tabletting speeds while optimizing consistent quality.

Sheffield BIO•SCIENCE

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A KERRY Group Business

ADVERTORIAL

Stäubli

www.staubli.com

Fast Moving Technology

With presence in 25 countries, Stäubli is recognized worldwide for providing unrivaled quality and innovative technology. Since 1982, Stäubli has led the development of innovative solutions to improve productivity, safety, and product quality in robotics.

Stäubli offers a comprehensive product range, including 4-axis SCARA and 6-axis robots for payloads of up to 250 kg. All robotic systems operate on the CS8 controller platform, which is perfectly adpated to robotics. Today, Stäubli Robotics is the leading-edge player in robotics around the world with its engineering as effective and dependable as its sales and services.

Stäubli Robotics provides high performance, innovative and flexible solutions to satisfy the requirements of each industry. Designed to work in the most hostile environments as well as cleanrooms, Stäubli robots demonstrate their efficacy under all conditions.

The New Stericlean Series of Robots

The clean, precise and highly accurate range of Stericlean six axis robots provide the ideal solution to the unique set of requirements that automation in pharmaceutical, medical, and life sciences industries demand.

Stericlean is the first fully VHP (Vapor Hydrogen Peroxide) resistant robot, providing fully automated operations in an isolator or cleanroom environment.

Stericlean Features:

Cleanliness
- ISO class 2/3 (SCR version) and class 3/4 (CR version) clean robots according to the 14664-1 standard
- Reduced risk of contamination

Speed and Precision
- Reduced handling time
- Higher throughput
- Precise and smooth motion

Work envelope
- More efficient cell layout
- Reduced motion to accomplish tasks

Additional features
- Special surface treatments on the arm
- System and user connections protected under the base of the robot
- Critical parts in stainless steel
- Specialized lip seals
- GMP (Good Manufacturing Processes) qualified

All Stäubli Robots Feature:
- Speed
- Precision
- Reliability
- fully enclosed structure

STÄUBLI

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Thomas Engineering

www.thomaseng.com

Since 1959, Thomas Engineering Inc. has been a leader in the supply of tablet coating equipment and tablet press punch and die tooling.

Our commitment to tablet manufacturing excellence is well demonstrated by our industry-leading Accela-Cota® systems. Far and away the most popular tablet coating system on the market, the Thomas Accela-Cota's fully perforated coating drum revolutionized coating applications in years past, and today, continues to set the standards for tablet coating with its unrestricted air flow, thermodynamic efficiency and integration. Designed to the most exacting standards, and created in accordance with GMP (Good Manufacturing Practice) regulations, each Accela-Cota offers unmatched levels of productivity, consistency and repeatability for your special requirements.

Our Accela-Cota family of products ranges from the small scale fully integrated sub-kilogram bench top Thomas Flex 05 tablet coater, to the industry's most versatile production scale Thomas Flex 500 batch tablet coater with 7 exchangeable drums, and the high capacity Thomas CTC Continuous Tablet Coater. Thomas Engineering has both the experience and the equipment solutions to accommodate all of your tablet production needs.

For more information about our fully integrated tablet coating systems and our tablet press tooling services please visit www.thomaseng.com or call 800-634-9910.

THOMAS ENGINEERING INC.

ADVERTORIAL

Veltek Associates, Inc.

www.sterile.com

Veltek Associates, Inc. has a complete line of sterile clean room polyester wipers including a dry wipe, alcohol wipes, sodium hypochlorite wipe, hydrogen peroxide wipe, lubricating wipe, polishing wipe and residue removing wipe.

All of Veltek's wipes are manufactured using the patented Asepti-Fill System® within a Class 100 (Grade A, ISO 5) area and use Focus-Edge® cutting technology allows for the most advanced non-shedding wipers in the industry.

- The **WipeDown®** wiper is a Class 10 dry wipe offering superior absorbency. It is laundered in ultra-filtered water of 45µ and dried in a HEPA filtered Class 1 air stream.
- The **ALCOH-Wipe®** wiper is available in three sizes and is saturated with Veltek's DE-CON-AHOL® WFI 70% IPA.
- The **Process2Wipe® IPA70** wipers saturated with 70% USP IPA and Water for Injection. They are ideal for both aseptic and non-aseptic wipe downs.
- The **HYPO-CHLOR®** wipes are sodium hypochlorite saturated wipes available in three concentrations and are ideal for both aseptic and non-aseptic wipe downs.
- The **STERI-PEROX®** wipes are hydrogen peroxide saturated wipes available in two concentrations and are designed for broad and intricate locations where the desire to reduce VOCs is required.
- The **DAS-Wipes®** are saturated with a stainless steel cleaner/lubricant with low remaining residues which allow them to be used in the aseptic manufacturing area.
- The **STEEL-BRIGHT®** wipes contain a stainless steel cleaner and are for the removal of chemical residues. They leave no residue making them idea for the aseptic manufacturing area.
- The **DECON-Clean®** wipes are saturated with a cleaning agent designed to remove residues from disinfecting agents as well as product residues left behind on critical manufacturing equipment.

WipeDown, Process2Wipe IPA70, HYPO-CHLOR, STERI-PEROX and DECON-Clean are all packaged in re-sealable bags of 20 wipes per bag, while the ALCOH-Wipe, DAS-Wipe and STEEL-BRIGHT wipes are available in individually packed wipers.

vai

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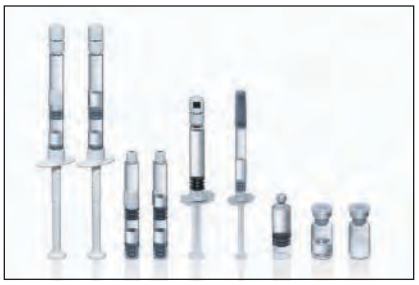
Vetter Pharma International GmbH

www.vetter-pharma.com



Filling your clinical development needs now also in Chicago

Vetter, a leading provider of aseptically prefilled drug-delivery systems, launched a new state-of-the-art facility at the Illinois Science + Technology Park in suburban Chicago. An expansion of Vetter Development Service, the Chicago site supports pre-clinical through phase II development projects. The 24,000-ft facility's functional areas include microbiology and chemical analysis lab; materials preparation; compounding; aseptic cGMP filling for vials, syringes, and cartridges; quality assurance; and seamless transfer to Vetter Commercial Manufacturing.

Early-phase work

Developed at the urging of Vetter's North American clients, the Chicago site supports small-batch, early-stage products. Vetter has extensive experience working with biologics and other complex compounds. Type of stopper or glass and degree of siliconization can potentially interact with a product's active ingredient. Matching drug product to delivery system and manufacturing process is critical. So is maximizing API. Vetter's state-of-the-art technology preserves API during the filling process, and its experience in the industry minimizes wasteful trial and error.

Expanding development services to Chicago

Vetter's new Chicago facility is an expansion of Vetter Development Service, which employs more than 100 personnel in Europe and the United States and supports customer products from preclinical development through market launch. Its service portfolio includes primary and secondary packaging development, process development, clinical manufacturing, pharmaceutical analysis, regulatory affairs services, and seamless product transfer to Vetter Commercial Manufacturing.

Vetter at a glance

Vetter is an independent international specialist in the aseptic filling of syringes, cartridges and vials. With approximately 2,400 employees worldwide, Vetter holds nearly 140 patents and has longstanding experience in working with regulatory authorities around the world.

Vetter's international success arises from its three interdependent divisions:

- Vetter Development Service specializes in taking complex compounds from preclinical development to regulatory approval and worldwide market launch.
- Vetter Commercial Manufacturing performs the entire production process, from compounding and aseptic filling to final product packaging.
- Vetter Solutions' innovative patented drug-delivery and anti-counterfeiting systems help clients to compete more effectively throughout the world.

For US inquiries please contact
+1-847-581-6888 or
infoUS@vetter-pharma.com

For EU inquiries please contact
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Waters has created the highest performing UPLC® ever engineered. Significantly improved chromatographic performance gives you more confidence in your results and allows you to get the most sensitivity from your mass spectrometer. But for the scientists who want answers to the most complex challenges, the ACQUITY UPLC® I-Class is simply about one thing. Opportunity. Learn more at waters.com/iclass

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ACQUITY UPLC I-Class System
Waters ACQUITY UPLC® I-Class System, the highest performing UPLC system ever engineered, takes UltraPerformance LC® separations technology to the next level. For scientists challenged by the most difficult separations, the ACQUITY UPLC I-Class features the lowest system dispersion and lowest carryover in the industry today. Low dispersion maximizes peak capacity thereby advancing chromatographic separations and optimizing the performance of any mass spectrometer. *www.waters.com/iclass*

Regulated Bioanalysis System Solution
Waters® Regulated Bioanalysis System Solution is a breakthrough LC/MS/MS system for bioanalysis that combines the latest in sample preparation, UltraPerformance LC® (UPLC®) separations technology and chemistries, tandem quadrupole mass spectrometry, and the UNIFI™ Scientific Information System. This first-of-its-kind, single-vendor system solution is tailor-made for bioanalytical laboratories and generates quantitative results quickly and accurately, maximizes uptime, reduces cost per sample, and helps bring projects to completion more quickly. Designed first and foremost with the needs of the bioanalytical scientist in mind, the Waters Regulated Bioanalysis System Solution ties together all the necessary components for streamlined bioanalysis of small molecule drugs and biotherapeutics. *www.waters.com/bioanalysis*

SYNAPT G2-S High Definition Mass Spectrometer
Waters SYNAPT® G2-S High Definition Mass Spectrometer represents a significant step forward in performance for High Definition Mass Spectrometry. The SYNAPT G2-S incorporates both high-sensitivity Waters® StepWave™ ion transfer optics and Triwave® ion mobility technologies along with a suite of new informatics tools to take qualitative and quantitative high resolution performance to a new level. SYNAPT G2-S provides a 30X improvement in signal intensity for mass spectral peaks, better than a 5X improvement in signal-to-noise, and up to a 10-fold improvement in limits of quantitation over previous-generation mass spectrometers. *www.waters.com/synaptg2s*

Xevo TQD Tandem Quadrupole Mass Spectrometer
Waters Xevo® TQD tandem quadrupole mass spectrometer is the most versatile technology platform in its class. It brings the Waters® design philosophy of Engineered Simplicity™ to routine quantitative LC/MS/MS analysis. *www.waters.com/xevotqd*

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MANUFACTURING EQUIPMENT & SUPPLIES

Culturing set

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

Quality-control system

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

Fluid-bed dryer bags

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

MANUFACTURING EQUIPMENT & SUPPLIES

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*

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*

Plunger-rod-inserting machine

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

MANUFACTURING EQUIPMENT & SUPPLIES

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*

Pharmaceutical robot

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

Detergents

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

MANUFACTURING EQUIPMENT & SUPPLIES

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*

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*

Membrane filter cartridges

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

MANUFACTURING EQUIPMENT & SUPPLIES

Clean-design mixers

Ross's double planetary mixers incorporate clean-design features to help users improve the efficiency of high-viscosity mixing processes. The mixers' helical blades prevent the product from climbing as it does in mixers with traditional rectangular stirrers. High-viscosity "HV" blades on Ross double planetary mixers feature a precisely angled helical contour that keeps material within the mixing zone at all times. **Charles Ross & Son Company,** *Hauppauge, NY • www.mixers.com • tel. 800.243.ROSS*

Rheometer

Brookfield's R/S Plus rheometer with direct-yield stress measurement is designed for quality control and research applications. The R/S unit has high flow-measurement capability, an increased speed range (i.e., 0.1 to 1000 rpm), control solution, and measurement sensitivity. The encoder is designed to provide control at low torque and shear rates, a precise static yield test capability, and more information for creep testing. **Brookfield Engineering Laboratories,** *Middleboro, MA • www.brookfieldengineering.com • tel. 800.628.8139*

Tablet-coating platform

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

OUTSOURCING & CONSULTING SERVICES

Contract research organization

MPI Research is a contract research organization for preclinical and clinical services targeting discovery, safety, bioanalytical, and analytical sciences. MPI Research has assembled a responsive staff with a mix of scientific knowledge and experience. The company stresses teamwork and strong and enduring sponsor relationships. MPI Research aims to be a high-performance, high-quality organization. **MPI Research,** *Mattawan, MI • www.mpiresearch.com • tel. 269.668.3336*

Outsourced services

Companies worldwide look to 3M Drug Delivery Systems for transdermal systems and components, as well as manufacturing solutions to help accelerate development and enable success. 3M aims to satisfy companies' transdermal-delivery needs, and its microneedle technology is designed to expand the range of transdermally delivered drugs. **3M Drug Delivery Systems,** *St. Paul, MN • www.3m.com • tel. 800.643.8086*

ROPACK
Contract Manufacturing & Packaging For Solid Oral Dosage

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*

OUTSOURCING & CONSULTING SERVICES

Chemistry outsourcing

Cambridge Major Laboratories is a global, service-based chemistry-outsourcing partner to the pharmaceutical and biotechnology industries. The company provides development and large-scale manufacturing services for active ingredients. A facility in the US complies with good manufacturing practice, and the company also maintains facilities in Europe. **Cambridge Major Laboratories,** *Germantown, WI • www.c-mlabs.com • tel. 262.251.5044*

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*

Outsourced services

Coating Place is a leader in services from Wurster fluid-bed formulation development to commercial manufacturing. The company performs bead layering, extrusion–spheronization, roller compaction, and capsule filling and tabletting. Coating Place processes both solvent and aqueous formulations. Its facilities are registered with the US Food and Drug Administration. **Coating Place,** *Verona, WI • www.encap.com • tel. 608.845.9521*

CLEANROOM EQUIPMENT & SUPPLIES

Sterile wipes

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

PACKAGING EQUIPMENT & SUPPLIES

Transfer packaging for prefillable syringes

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

Packaging solution

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

PACKAGING EQUIPMENT & SUPPLIES

Analytical system

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

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*

Analytical system

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

LABORATORY EQUIPMENT & SUPPLIES

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*

On-line TOC analysis

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

LABORATORY EQUIPMENT & SUPPLIES

Laboratory blenders

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

Chromatography products catalog

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

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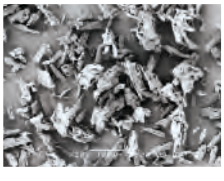

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in the US, only 10% of those funds have come from public sources, according to a 2006 report from the US Department of Health and Human Services. The department recognized the need for increased public investment and called for the creation of a Federal Initiative for Regenerative Medicine, similar to the semiconductor manufacturing technology (SEMATECH) public-private consortium model that accelerated the growth of the semiconductor industry in the 1980s and 1990s (1).

National strategy

As the Obama administration touts its innovation strategy as a tool for promoting economic growth, the industry is also recognizing the need for a national strategy for regenerative medicine to sustain investment in this sector and raise the profile of regenerative medicine as one of America's fastest growing innovative industries. The Alliance for Regenerative Medicine has drafted a strategy that is supported by industry to rival bold initiatives that have been announced by China and other countries. The essential elements of the national strategy include:

- Creation of a coordinated plan among the various federal agencies overseeing regenerative-medicine programs and policies
- Development of incentives that will stimulate greater private investment in regenerative medicine technologies and therapies
- Increased federal funding for regenerative-medicine research with a particular emphasis on promoting public–private partnerships
- A predictable regulatory review and approval process
- A reimbursement framework that will help companies plan for and communicate the commercial potential of their products.

The Alliance developed this plan to provide a strategic framework that will complement the legislative proposals included in the Regenerative Medicine Promotion Act of 2011, which the US House of Representatives introduced as H.R. 1862 in May 2011. This legislation calls for the creation of a Regenerative Medicine Coordinating Council among federal government stakeholders, establishment of different funding mechanisms for public–private research projects and preclinical work needed to file an investigatational new drug apppplication, and increased funding for regulatory science research at FDA. The Regenerative Medicine Promotion Act of 2011—along with the national strategy—are essential to US efforts to maintain international leadership in healthcare innovation.

Reference

1. HHS, "Future of Regenerative Medicine," (HHS, 2006), www.hhs.gov/reference/newfuture.shtml. **PT**

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Regenerative Medicine: The Need for a National Strategy

Elizabeth West

US support of regenerative medicine is essential for maintaining a lead on healthcare innovation.

Regenerative medicine provides an ideal opportunity for public investment in an industry that will help the United States maintain its global technological leadership and facilitate needed advances in healthcare. The industry is revolutionizing treatments of numerous chronic diseases, including diabetes, Parkinson's disease, ALS, heart failure, and different types of cancers, by focusing on using living cells to repair tissue and treat the underlying causes of disease. The potential of regenerative medicine to lead to disease-altering treatments for these conditions is real and, in some cases, may include the complete regeneration of damaged tissue and organs.

Although full-organ replacement technology is likely decades away, dozens of innovative, entrepreneurial firms are advancing therapies in clinical trials for the treatment of costly diseases, such as critical limb ischemia, myocardial infarction, and spinal-cord injury, to name a few. Not only do these therapies represent an opportunity to drastically improve the current standard of care, but they may also provide billions of dollars in long-term cost savings for treatments of these chronic diseases. The potential savings from regenerative medicine treatments for the US alone in terms of the direct costs associated with five prevalent chronic diseases—late-stage Parkinson's disease, new cases of spinal-cord injury, heart failure, stroke, and insulin-dependent diabetes—is approximately $250 billion a year.

The potential to lead to disease-altering treatments is real.

Global support

Other nations have also recognized the potential of regenerative medicine and are keen to grow their capabilities in this field. China's Ministry of Science and Technology, for example, allocated more than $290 million dollars for stem-cell research during the period 2006–2010. More than 75% of those funds are being used for product development. The government has prioritized stem-cell and regenerative-medicine research by placing approximately 300 researchers in 30 institutions to focus on key strategic areas, including nerve injury and functional reconstruction of tissue. Japan, the United Kingdom, and Australia have national efforts targeting regenerative medicine and cell therapy priority areas in medical innovation as well.

US strength

Although international investment in regenerative medicine is intensifying, many research institutions and companies leading the efforts to develop new therapies are based in the US. The infrastructure required to manage these programs is significant and contributes to job growth and investment that supports many regional economies. California has led the charge with the creation of the California Institute of Regenerative Medicine (CIRM) through a statewide ballot measure that provided $3 billion in funding for stem-cell research at California universities, research institutions, and therapeutic development companies. CIRM recently released economic impact data estimating that its first $1.1 billion in grants will create 25,000 jobs and $200 million in new tax revenue for California through 2014.

Despite the promise of regenerative medicine in economic development and for improving the healthcare system, companies in this sector still face numerous challenges that are hindering their ability to develop products for patients. These obstacles include insufficient funding for product development and clinical trials, an unclear regulatory pathway for new technologies, inconsistent reimbursement policies, and a general lack of awareness of the potential for regenerative medicine to help us address long-term healthcare costs. Although $4 billion has poured into this growing sector

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Your opinion matters.
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Elizabeth West is director of programs at the Alliance for Regenerative Medicine, ewest@alliancerm.org.

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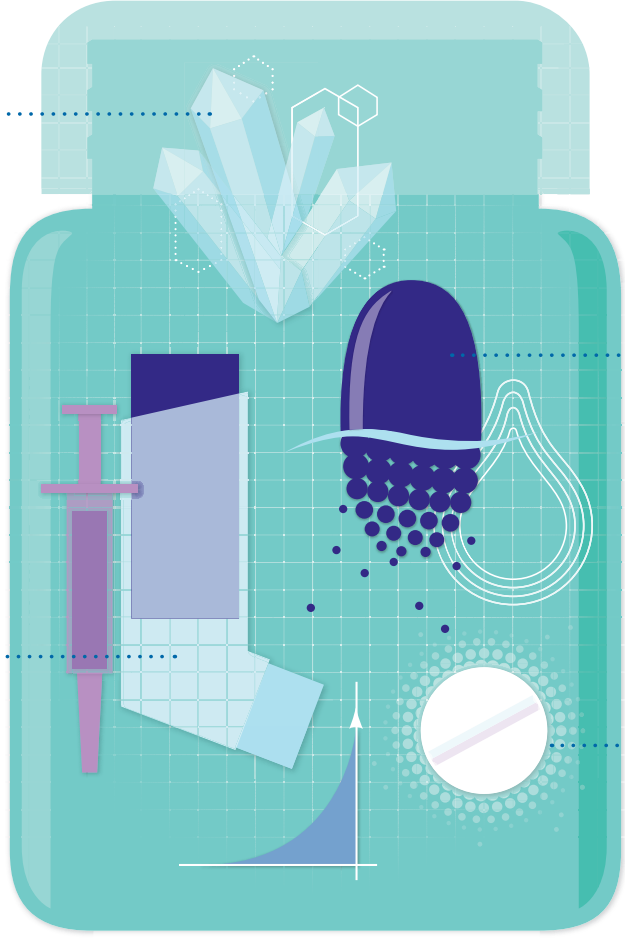

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