Volume 37 Number 4
PHARMACEUTICAL TECHNOLOGY
APRIL 2013
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APRIL 2013 Volume 37 Number 4

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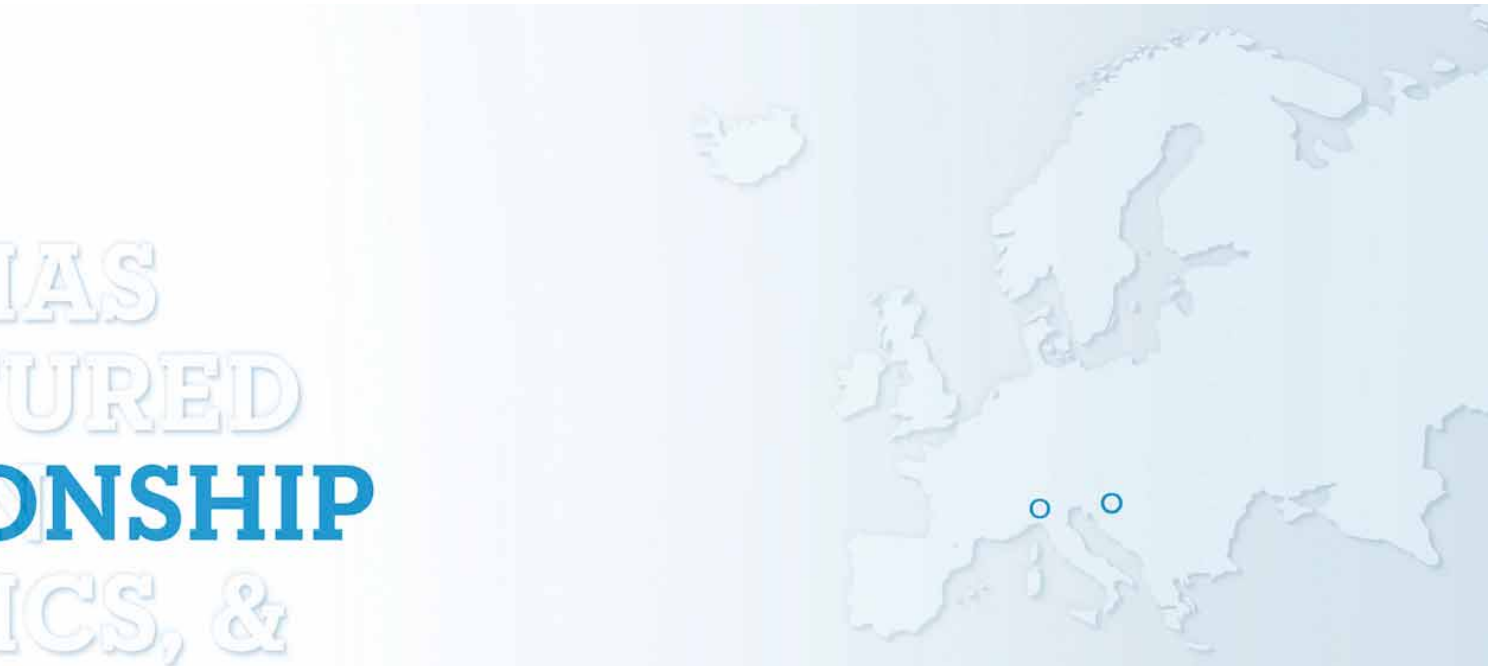

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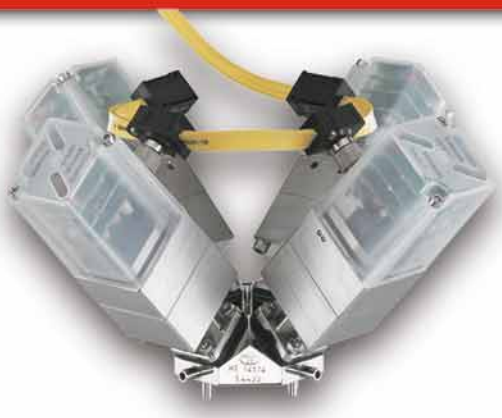

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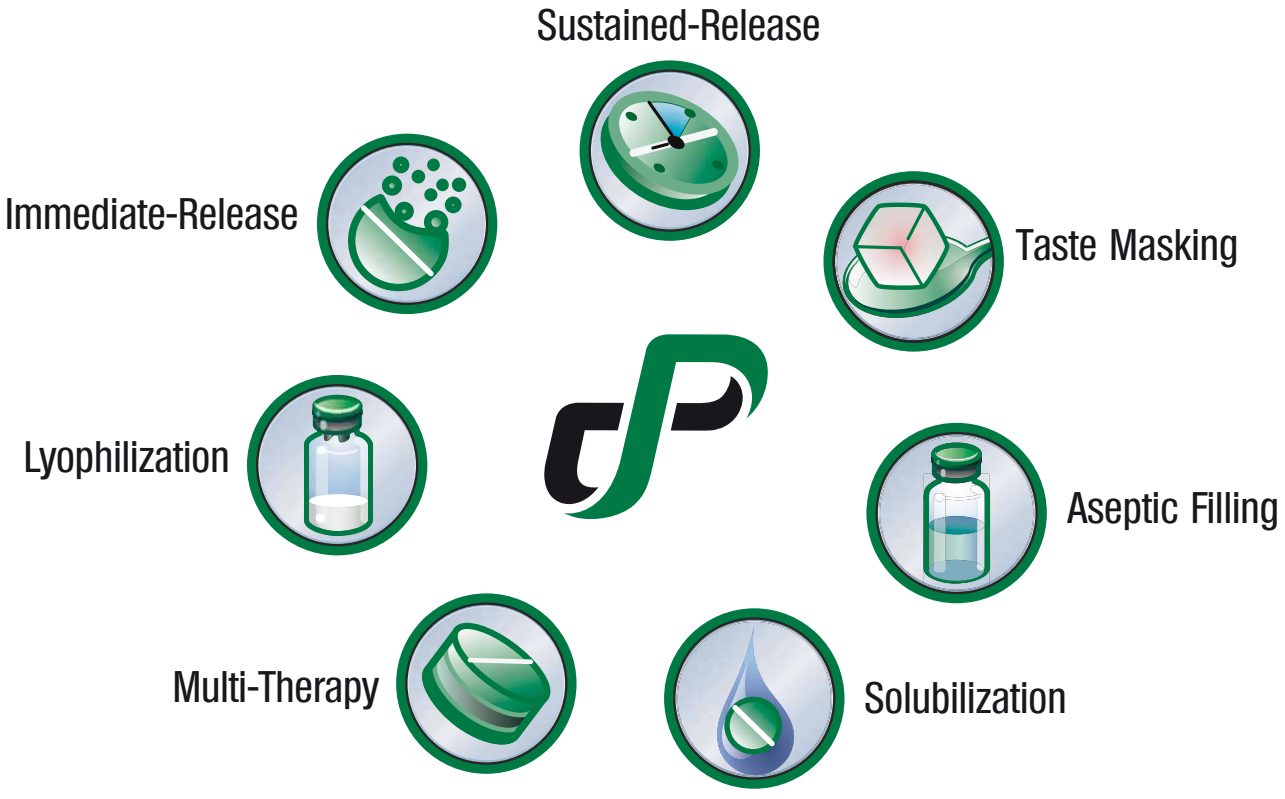

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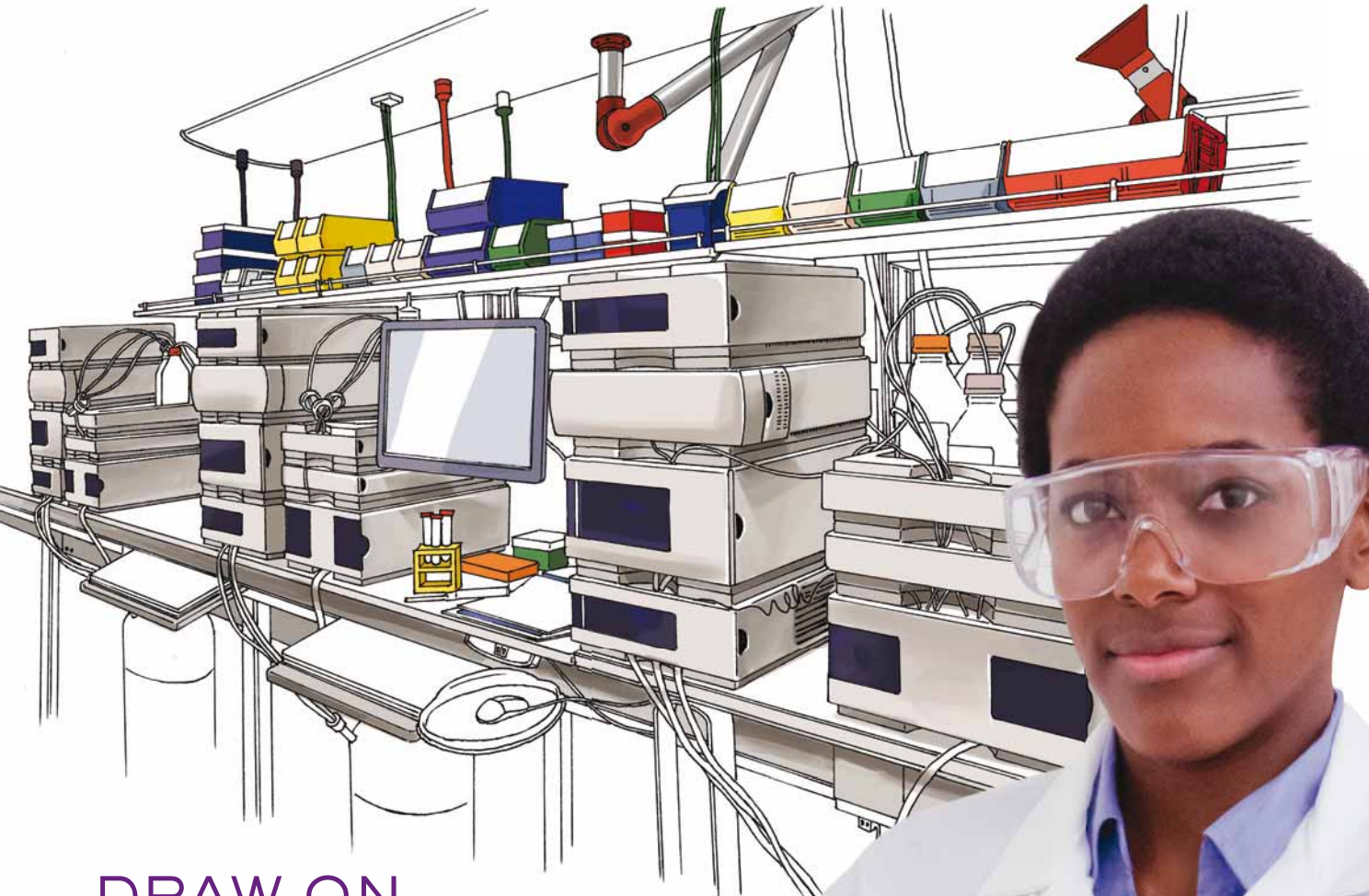

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On the cover

COVER STORY

56 PAT and Process Control in Solid-Dosage Manufacturing

Industry is moving toward closed-loop control of continuous processing.

Illustration by Dan Ward
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FEATURES

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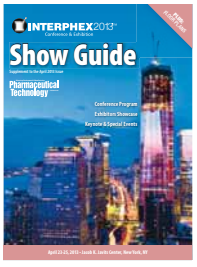
Be sure to check out this month's INTERPHEX Show Guide 2013.



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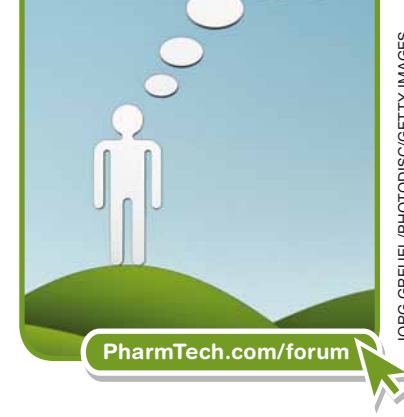


JORG GREUEL/PHOTODISC/GETTY IMAGES

INTERPHEX 2013: Aligning with Industry's Needs

Russ Somma

Conference and exhibits provide a meeting place for professionals to exchange ideas.

The pharmaceutical industry continues to move ahead with its trajectory being tweaked by various outside forces. The highly regulated nature of our industry is a major contributor, while the need to do more with less continues to vex our everyday efforts. These factors are acutely realized when we congregate with fellow industry professionals at society and professional meetings. I use these interactions to explore the next big need for my clients as well as to craft a strategy that will help address these needs. INTERPHEX 2013, while being a continuation of the journey described by Bob Stewart last year, is also a realization of this "group thinking" fueled by current needs and pressures of our industry. It takes only a quick glance at the conference agenda and list of exhibitors to fully appreciate this synergy.

The customized conference content of INTERPHEX 2013 is the product of group thinking carried out in a structured environment, which we refer to glibly as the advisory board. When you ask 15 industry professionals (the board) from across all sectors of our industry, you are guaranteed of getting valued input as well as things that are current and need to be addressed. The five conference tracks—regulatory quality assurance/quality control, product development, facility and process design, manufacturing and packaging, and supply chain—were pressure tested at INTERPHEX 2012 and have been leveraged effectively here for INTERPHEX 2013. Several select topics will provide high value input for attendees.

Current Development Best Practices for IR and MR Dosage Forms will be discussed by Glenn Van Buskirk and will touch upon aspects of the current effort to address the needed updates for FDA guidance in the area of post-approval changes. The industry has regularly used the Scale-Up and Post-Approval Change (SUPAC) guidances that were issued more than a decade ago. The widespread use of these guidances along with current industry need has brought about a rethinking in this area and will produce a work product that will be a reliable and time-proven asset.

A keynote address, Reorganizing for the Future: Succeeding in the New Pharmaceutical Industry, will be given by Rajesh Nair from his perspective as president of Indegene. With a track record of having worked and consulted for many firms, Indegene has assisted various companies as they navigate through strategies to become more agile as they bring products to market and leverage existing product lines through a successful lifecycle.

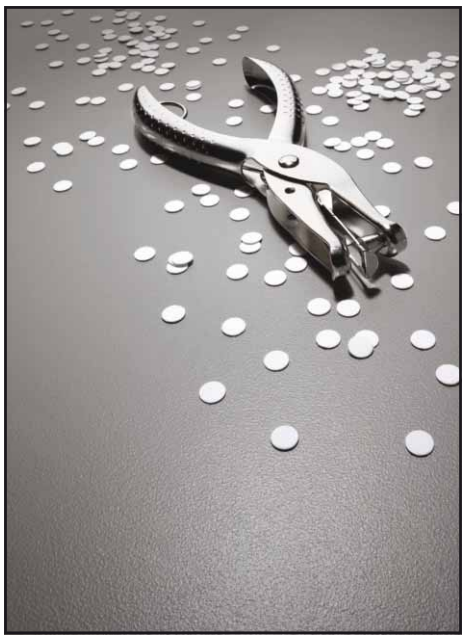
A team from Duquesne University lead by Jim Drennen and Benoit Inge has assembled a must-see session that will take the attendee through a practical utilization of aspects of quality by design as well as the application of key process control tools such as PAT. This will be followed by a panel discussion lead by Carl Anderson, also from Duquesne University. The panel will be case study-driven with experts from regulatory, development, quality, and the consulting sectors. The panelists will share their views as well as address must-have answers from attendees.

Combination products along with information-rich case studies will be presented from leading medical device manufacturers. David Armbruster from DePuy Synthes and Roy Fennimore from Johnson & Johnson will walk the attendees through each of their sessions. David will discuss the aspects of product realization from concept through manufacture while Roy will detail technology transfer for design control of convergent products.

A high priority has been placed on the "meeting place" that allows professionals to gather and exchange ideas. As highlighted by Bob Stewart, "there is a need to connect, face-to-face, in order to teach, to learn, to do business and to know each other better. Personal collaboration is critical to the industry INTERPHEX serves, and collaboration can begin with a conversation, with a meeting." INTERPHEX has established just such a meeting place and forum.

The INTERPHEX team looks forward to meeting you at the Javits Center in New York City on April 23–25, 2103. Let us know your thoughts, at any time. We intend to serve the industry and continue our mission to make INTERPHEX the venue to learn it, hear it, see it, touch it, and procure it. **PT**

Russ Somma, PhD, is president of Somma Tech, LLC and an INTERPHEX conference consultant.



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Prescribing Caution for Biosimilars

James C. Greenwood

Sound policies are needed to govern the substitution of interchangeable biologics.

In statehouses around the country, lawmakers are beginning to address the complexities of cutting-edge biotech drugs and the regulatory issues related to the interchangeability of biosimilar medicines. These legislative efforts represent a significant step in recognizing the important and complex role biologic medicines play in the future of healthcare and chronic disease management. They are also a necessary measure to ensure that patients and their physicians remain in control of their medical treatment decision-making as the market for complex biologics evolves over the next several years.

Biosimilars are manufactured with the goal of closely mirroring the composition and treatment profile of an innovator biologic product, but are produced without access to the innovator's proprietary manufacturing processes.

Two biologics made using different cell lines and manufacturing processes will rarely, if ever, be exactly the same, hence the name "biosimilar." Simply put, biosimilars are not generics, and those suggesting otherwise are incorrect. Thus, current state laws governing the substitution of generics are not, and should not be, automatically applicable to biosimilars.

James C. Greenwood is the President and CEO of the Biotechnology Industry Organization (BIO).

Patients and physicians managing chronic conditions are generally aware of which treatments work best in their unique circumstances. Therefore, the decision to change to a biosimilar treatment is best made by doctor and patient. However, at a minimum, providing notice to the prescribing doctor and patient ensures everyone in the treatment continuum is informed of decisions to switch to a different biologic drug, either at the pharmacy level or due to insurance coverage guidelines.

The decision to change to a biosimilar treatment is best made by doctor and patient.

Until recently, there was no pathway for the development and approval of biosimilar products in the United States. The US Food and Drug Administration is currently developing such a pathway. Even after it is enacted, the policy on whether one biologic product may be substituted by dispensers when a different biologic product was prescribed will continue to be governed by state law.

At present, most state laws need to be updated to address the commercialization and distribution of new biologic products and their biosimilar competitors, which are set to enter the marketplace over the next few years. Sound policy in each state outlining the parameters for safe substitution of interchangeable biologics is the best option to ensure patients have access to the most effective and appropriate treatments possible.

Recognizing the authority US states have over biosimilar and interchangeable biologic medicines, Biotechnology Industry Organization (BIO) developed five principles on biologic substitution that we believe should be considered by all states when evaluating biosimilar legislation. Briefly stated, these principals are:

- Substitution should occur only when FDA has designated a biologic product as interchangeable
- The prescribing physician should be able to designate a prescription as not substitutable
- The prescribing physician should be notified of the substitution if one occurs after the prescription is ordered
- The patient, or the patient's authorized representative, should, at a minimum, be notified of the substitution
- The pharmacist and the physician should keep records of the substitution.

These principles strike the appropriate balance of preserving the physician-patient relationship, protecting patients, and promoting a competitive market for biologic therapies. We welcome the opportunity to further discuss this issue with lawmakers as they seek to address vital drug safety measures that accompany this cutting-edge technology. **PT**

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HITTING THE HEADLINES

AstraZeneca Announces an Additional 2300 Layoffs

AstraZeneca announced further downsizing in response to an expected period of declining revenues in the face of patent expirations. The company will eliminate 2300 positions in sales and general administration. The new announcement brings the total headcount reduction to approximately 5050 over the 2013–2016 period.
PharmTech.com/AstraZenecaRestructuring

IPEC Releases Revised Excipient Information Package Guidance

The 2013 Excipient Information Package (EIP) User Guide is now available for free download from the International Pharmaceutical Excipients Council (IPEC)-Americas website. The revised guide updates the 2005 version.
PharmTech.com/EIPguidance

European Patent Filings Up, But Pharma Stays Flat

While the number of patent filings at the European Patent Office in 2012 increased by 5.2% over 2011, pharmaceutical-based patents remained flat, and biotechnology patents dropped slightly. The EPO reports 5377 filings for pharmaceutical patents in 2012, compared to 5364 in 2011. Biotechnology-based patents dropped 4.3% from 5550 in 2011 to 5309 in 2012.
PharmTech.com/EuroPatentsUp

AstraZeneca's Crestor Patents Ruled Invalid in Australia

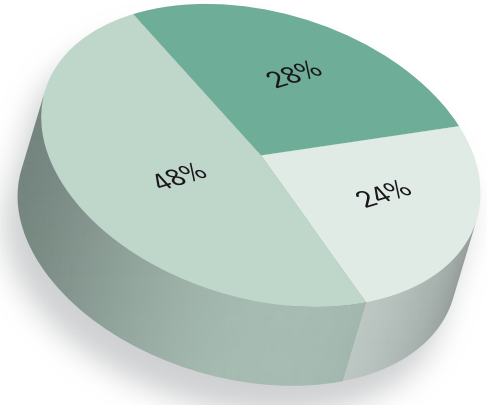
AstraZeneca's three patents protecting Crestor (rosuvastatin) have been ruled invalid by the Federal Court of Australia under challenges from Apotex, Watson Pharma, and Ascent Pharma. The patents include a formulation patent expiring in 2020, a patent related to the use of rosuvastatin for the treatment of heterozygous familial hypercholesterolemia, which will expire in 2021, and a patent for treating hypercholesterolaemia with an expiry date of 2020.
PharmTech.com/AZPatentsAustralia

Roche and BioLamina Collaborate on Novel Cell Culture Systems

Roche and BioLamina have entered into a research and development agreement to jointly develop new cell culture systems for various applications, including stem cell research. The collaboration will assess laminin-based *in-vitro* cell culture matrices that can offer physiological microenvironments for living cells.
PharmTech.com/RocheCellCulturePact

READERS THINK THAT...

Which of the following has had the most significant advances in PAT over the last 5 years?



View more poll results at:
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First Biologic Approved in the EU for Gouty Arthritis

Ilaris (canakinumab), a selective, fully human, monoclonal antibody that inhibits interleukin-1 beta (IL-1 beta), has been approved in the EU for symptomatic pain relief in patients suffering from gouty arthritis whose condition cannot be managed with current treatments.
PharmTech.com/EUArthritisBiologic

Roche Chairman to Step Down in 2014

Franz B. Humer, chairman of the board of directors of the Roche Group, will not stand for re-election to the Board in 2014.
PharmTech.com/RocheChairmanStepsDown

MOST TWEETED

- DaiichiSankyo condemns falsely represented product being sold online to consumers in Malaysia and Indonesia. ow.ly/iPcFl
- Sales of traditional drugs fell for first time according to Express Scripts report; attributed to patent expirations. ow.ly/ivwDE
- AstraZeneca to cut 1600 positions, consolidating R&D capabilities in Cambridge, UK; Gaithersburg, Md. in the US; and Mölndal, Sweden. ow.ly/jd7IO

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INDUSTRY NEWS

- Ajinomoto has agreed to acquire the CDMO Althea Technologies for approximately $175 million. The acquisition's closing is expected to be complete in April 2013, at which point Althea will become a fully consolidated subsidiary of Ajinomoto.

- The CDMO DPT Laboratories received notification from FDA on Feb. 19, 2013, that signaled the completion of the agency's evaluation of DPT's corrective actions taken at its Lakewood, N.J., facility in response to a Warning Letter received on Aug. 27, 2012. In addition, the letter communicated that in the view of FDA, the Lakewood site is compliant with FDA regulations.

- FDA expanded the approved use of Stivarga (regorafenib) to treat patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to other FDA-approved treatments for this disease.

- Merck announced that the Phase III Centric trial of the investigational integrin inhibitor cilengitide did not meet its primary endpoint of significantly increasing overall survival when added to the current standard chemoradiotherapy regimen (temozolomide and radiotherapy). Centric included patients with newly diagnosed glioblastoma and methylated O6-methylguanine-DNA methyltransferase gene promoter status.

- The CMO Neuland Laboratories has formed a manufacturing collaboration with Tokyo-based API Corporation (APIC), a healthcare unit of Mitsubishi Chemical Holdings Group that produces APIs, intermediates, investigational new drugs, fine chemicals, and reagents. Under the agreement, API Corporation is making an investment in Neuland's facilities that will provide APIC with dedicated capacity for meeting the needs of its customers. The facilities will be operated by Neuland's employees and the two companies will share oversight and management responsibilities.

- The Parenteral Drug Association (PDA) announced that three high-level regulators from the US and Europe will speak at the 2013 PDA/FDA Process Validation Workshop, May 20–21, 2013, at the Hyatt Regency in Bethesda, Maryland. The speakers include: Jeffrey Baker, deputy director, office of biotechnology, CDER, FDA; Lina Ertle, quality assessor, ANSM (France); and Patrick Swann, deputy director, division of monoclonal antibodies, CDER, FDA.

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ON THE BLOG

"After less than a year on the job, the head of FDA's Office of Generic Drugs (OGD) has announced his departure, a sign that all is not well with plans for major organizational changes at the Center or Drug Evaluation and Research (CDER)."
Jill Wechsler
PharmTech.com/Wechsler

"The federal budget sequestration mandate went into effect Mar. 1, 2013, and, initially, the impact was fairly muted. Federal agencies, including FDA, launched initiatives to comply with the mandated 5% across-the-board cut in spending (in reality a 9% cut that exceeds $200 million) to minimize the impact on basic operations."
Jill Wechsler
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Viral Vaccine Manufacturing

A Q&A with Tony Hitchcock, head of manufacturing at Cobra Biologics.

Production of viral vectors for vaccines poses a distinct set of challenges. Tony Hitchcock, head of manufacturing at Cobra Biologics, spoke with *Pharmaceutical Technology* about trends and challenges of manufacturing viral products in cell culture.

PharmTech: With the approval of Novartis' mammalian cell-produced influenza vaccine in 2012, production methods for viral vaccines seem to be undergoing a shift from egg-based manufacturing to cell-based. What advances in recent years have enabled this transition and what challenges still remain?

Hitchcock: The production of viral vaccines has been performed in egg-based systems for many years, and it is clear that while significant developments in the production of viral vectors from cell culture-based systems have advanced, many existing vaccine products will continue to be produced in this manner. For example, GlaxoSmithKline has just introduced a quadravalent flu vaccine from eggs, and Medimmune has invested significantly in the automation of eggbased processes at their UK facilities. These developments would indicate that for products, such as seasonal flu vaccine, existing production routes will be retained for the foreseeable future.

For manufacturers of products such as flu vaccines, while significant investment from national governments among others has been put in place to develop a cell-based production process to enable a response to pandemic flu, it is clear that egg-based processes are still sufficiently productive and cost effective to meet needs for seasonal demand. Combined with long-term safety profiles and in-place manufacturing capabilities, the drivers for adopting cell-based processes are not sufficient to justify their adoption. It is also clear that becasuse of the specialist nature of eggbased production facilities, the majority of manufacturing will remain as an inhouse activity with limited opportunities for contract manufacturers in this field.

The real opportunities for the production of viral vectors from cell culture-based processes arguably lie with novel vaccine products.

In January 2013, however, FDA approved Protein Science Corporation's Flublok vaccine, another non-egg-based influenza vaccine, which is potentially the sign of things to come. It will be interesting to see what the up the uptake of this product will be compared with the existing egg-based products, and how the large pharma companies respond to this.

The real opportunities for the production of viral vectors from cell culturebased processes arguably lie with novel vaccine products, where there are no historical safety profiles in place. Other opportunities lie with products where eggbased systems are unsuitable, or where technical or product safety issues mean alternative approaches need to be sought to meet demands in terms of quantities of material or to achieve required levels of process robustness.

PharmTech: What are the risks associated with using cell-based manufacturing for vaccines, and how are these risks typically addressed?

Hitchcock: The potential risks with cell-based processes can be split into intrinsic and process-related. In terms of intrinsic risks, these will lie with the origin, purity, and design of the viral vector and producer cell line. Process-related risks will lie with the potential to introduce adventious agents/viruses into the process stream. Unlike the production of protein products from mammalian sources, it is clearly not possible to introduce validated viral inactivation or removal steps to mitigate these risks. Addressing these requires application of GMP principles and approaches to development programs at a very early stage, focusing on the history, purity, and stability of the viral vector. It is now commonplace for viral vectors to be rescued from synthesised plasmids, allowing for absolute traceability of the viral vector and full sequencing to be performed of the plasmids and resulting viral product. Stability studies can also be performed to demonstrate genetic stability of vectors at an early stage of development.

With regards to producer cell lines, it is essential that the origins are known and that they are free from adventious agents and that generation of cell banks for both process development as well as GMP production works. Additionally, there is clearly a need for maintenance of segregation throughout development programs to prevent contamination of viral stocks and cell banks. **PT**

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REGULATORY **ROUNDUP**

FDA targets compounders

In response to complaints that FDA did not shut down the New England Compounding Center before its contaminated injectables killed and sickened hundreds of people, the agency has launched a broad inspection program of "high-risk" pharmacy compounders. The agency is visiting approximately 30 compounding pharmacies over several months, targeting facilities engaged in large-scale production of sterile products, particularly those with a history of violations and adverse event reports. FDA posted the results of its first four inspections last month, citing a range of lapses and faulty operations likely to lead to microbiological contamination. The agency has coordinated the inspections with state regulators, which will take enforcement action where FDA lacks authority. Similarly, surprise inspections of 37 specialty pharmacies by Massachusetts health authorities uncovered serious violations of state regulations and prompted the shutdown of 11 operations.

At the same time, manufacturers are pressing for legislation to strengthen FDA authority over compounders engaged in illegal drug production. Hospitals and veterinarians, however, are wary of new rules that could block access to specialized therapies. The prospects for compounding legislation recently gained momentum when the International Academy of Compounding Pharmacists signaled support for stronger FDA regulation of large-scale pharmacy operations.

Biosimilar battles

While FDA waits for the first biopharmaceutical manufacturer to file a biosimilar application, the fight is escalating over how these therapies will be tested, regulated, and dispensed. Abbott Laboratories is objecting to FDA approval of any biosimilar based on a reference drug approved before March 2010, when legislation was enacted authorizing these products. And just in case FDA ever decides that a biosimilar is interchangeable with the reference drug, innovator firms are backing bills in state legislatures to block pharmacy substitution of such products. This issue is pitting pharmacists against biotech manufacturers in Colorado, Mississippi, and other states. Meanwhile, Amgen unveiled an aggressive biosimilar development plan that focuses on leading cancer therapies, and Merck announced a new partnership with Samsung to develop biosimilars, after pulling back from earlier arrangements. FDA is meeting with potential biosimilar producers and working to finalize a development pathway, but the road to market remains rocky.

Spending drops for drugs, soars for biologics

US outlays in 2012 for conventional drugs dropped for the first time ever, according to Express Scripts, largely due to a steady rise in generic drug use. But this 1.5% decline, as reported in Express Scripts' annual Drug Trend Report, was offset by an 18.4% jump in spending on specialty medications, led by treatments for rheumatoid arthritis, multiple sclerosis, cancer, and HIV. Two new products drove up outlays for hepatitis C treatments by 34%, while spending rose 23% for therapies for inflammatory conditions. Similarly, new cancer medications to treat unique genetic profiles boosted spending in this category. These figures on specialty drugs would be much higher if they included medications delivered in hospitals and clinics, where half of treatment takes place.

Meanwhile, ever-growing use of generic drugs, largely due to the "patent cliff" affecting several blockbuster medications, dropped unit costs for several key categories. The nation spent the most on diabetes treatments, and outlays rose 14% on therapies for attention disorders. The full report is available at *www.DrugTrendReport.com*. Further insight on specialty drug management is available in an advisory on formulary submissions for these products from the Academy of Managed Care Pharmacy (www.amcp.org.).

CDER plans quality office

FDA's Center for Drug Evaluation and Research (CDER) plans to establish a new Office of Pharmaceutical Quality to coordinate agency and industry efforts to avert drug shortages, tackle global supply issues, and ensure industry compliance with the rules. CDER Director Janet Woodcock has mentioned this change in recent months, and Commissioner Margaret Hamburg made it official in her February speech to the Generic Pharmaceutical Association. Hamburg said the goal is to "improve consistency and regulatory certainty across the wide span of drug quality review," but not to change current GMP requirements. The tentative plan is to shift some parts of CDER's Office of Compliance into this new home for the current Office of Pharmaceutical Science.

Drugs in the water

Researchers continue to find that even small traces of pharmaceuticals in rivers and streams can have harmful effects on fish, but it's not clear what to do about it. The latest evidence comes from a study published in *Science* magazine by Swedish researchers who reported unusual harmful behaviors in perch exposed to very high concentrations of the anti-anxiety drug oxazepam (1). Other studies have revealed similar effects of antidepressants on minnows and of pharmaceutical ingredients on sexual characteristics of fish in France. Although there's much talk about improving disposal of unused medicines, many authorities find drug ingredients enter waterways primarily through sewage systems. That has prompted calls for better water treatment methods, along with further research on drug impact on water life.

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Manufacturers Under Pressure to Manage Painkillers

Opioid abuse generates calls for efforts to curb distribution, develop abuse-resistant formulations.

Abuse and misuse of prescription drug painkillers is soaring, responsible for more than 16,500 deaths in 2010, according to the Centers for Disease Control and Prevention (CDC). More than 250 million opioid prescriptions were filled in 2009, fueling a $9 billion market. Limiting opioid abuse is the most crucial public health issue for the Center for Drug Evaluation and Research (CDER) at FDA, said CDER Deputy Director Douglas Throckmorton in December 2012 at an industry conference. FDA seeks stronger warning labels and is encouraging development of abuse-deterrent formulations of long-acting opioids. Yet, Throckmorton notes the challenge of assuring patient access to these crucial drugs while reducing the "epidemic of abuse and misuse." This dilemma reflects a split in the medical community: pain specialists plead for ready access to needed medications for more than 100 million adults with chronic pain, while a growing number of experts back curbs on prescribing to curtail abuse. A key question is whether long-term treatment with opioids for pain is safe and effective, compared to use of these drugs for short-term relief.

The challenge is to assure patient access to these crucial drugs while reducing the epidemic of abuse.

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The opioid crisis also has drawn attention of Congressional leaders. The Senate Finance Committee launched an investigation in May 2012 of financial ties between opioid manufacturers and pain experts, looking for links between pharma industry money and the surge in inappropriate drug use. Sen. Joe Manchin (D-WV) sought to add stronger controls on certain opioids to last year's FDA Safety and Innovation Act (FDASIA), but backed off when FDA promised to address the issue this year. The development of new opioids with anti-abuse features also is spurring legislative proposals to block generic versions of older, easily tampered products.

Push for controls

FDA's immediate task is to weigh the scientific and medical merits of a proposal from the Drug Enforcement Administration (DEA) to impose stricter controls on drugs such as Vicodin (combination of hydrocodone and acetaminophen). DEA initially petitioned FDA in 2004 to evaluate evidence for reclassifying hydrocodone combination products from schedule III to schedule II under the Controlled Substances Act (CSA). This "upscheduling" would impose more stringent recordkeeping and storage requirements on 81 marketed combination medicines, virtually all of which are generic drugs. Schedule II prescriptions cannot be refilled or phoned in by doctors, and nurse practitioners and physician's assistants can't write scripts. The fear is that going to the doctor every three months for a new prescription could overburden individuals who are coping with chronic pain.

FDA rejected DEA's initial proposal, questioning whether the schedule change would make a real difference, considering the rampant abuse of opioids such as OxyContin and morphine that already are schedule II. DEA has come back with additional data on the surge in opioid-related deaths and hospitalizations, which has generated a groundswell for action. FDA sought advice on DEA's proposal from its Drug Safety and Risk Management Advisory Committee at a January 2013 meeting (rescheduled from October 2012 due to Hurricane Sandy). FDA safety experts and representatives of medical organizations analyzed DEA's research, while dozens of family members and medical practitioners described their experiences with drug-induced deaths and ruined lives.

Opposition to DEA's proposal came from the Generic Pharmaceutical Association (GPhA), which predicted supply-chain problems as manufacturers and wholesalers face requirements for larger vaults and new systems for storing controlled ingredients and finished goods. Pharmacists complained about a host of costly new security procedures, while practitioners predicted access problems for patients suffering from cancer, trauma, and post-operative pain. Despite FDA skepticism about the policy change, the advisory committee voted 19-10 in favor of DEA upscheduling, and FDA is expected to follow the panel's advice.

These issues were re-examined a week later at a February FDA public hearing on proposals to add stronger

labeling and warnings on opioid painkillers. Physicians for Responsible Opioid Prescribing had petitioned FDA to revise labels to limit opioid treatment to 90 days and to patients with "severe" and not "moderate" pain. Again, dozens of stakeholders testified on abuse and access issues. Family members of addicts complained that existing labels fail to adequately inform doctors or patients of the severe risks of the drugs; pain specialists opposed arbitrary limits, emphasizing the need for flexibility to treat patients based on individual needs. There was discussion about whether a drug track-and-trace system, using serialization to identify individual units, could curb illegal opioid distribution. Pharmacists supported this approach, along with use of electronic medical records and drug monitoring programs to identify dangerous drug use.

New formulations

Another strategy for curbing opioid abuse is for manufacturers to develop extended-release pain medications that resist tampering and misuse. FDA issued draft guidance in January 2013 that advises manufacturers on the types of studies needed to demonstrate anti-abuse effectiveness and explains how the agency will evaluate safety data and approve labeling for such products (1). The document describes how data could support a range of claims in labeling: that a product provides a barrier to abuse, blocks opioid effect when manipulated, leads to meaningful reduction in abuse, or demonstrates reduced abuse in the community.

The success of newer, tamper-resistant products, however, raises a much trickier issue for FDA: whether to block generic copies of earlier opioids that are more easily abused. Perdue Pharma gained approval in 2010 for a reformulated version of OxyContin that was more difficult to crush or dissolve and now wants FDA to rule out generic versions of its original product. Endo Pharmaceuticals has sought similar protection for an improved version of Opana.

Commissioner Hamburg clarified in a January letter to Congressional leaders that FDA has authority to require

generic opioids to adopt new tamper-resistant formulations, but only if the agency determines that such newer products will "significantly deter abuse", which FDA has yet to do (2). Hamburg hopes to head off legislation that would block FDA approval of generic versions of abuse-prone medicines, but recognizes that brand manufacturers are unlikely to develop new tamper-resistant products if cheaper versions of old drugs come to market.

At the same time, manufacturers may find it difficult to gain FDA approval of new painkillers without anti-abuse features, as seen in delayed action on approving Zohydro, a high-dose, long-acting hydrocodone product from San Diego-based Zogenix. An advisory committee rejected the drug last December, expressing fears that Zohydro could lead to dependence and would be highly attractive to illicit users.

Meanwhile, FDA is being more proactive in the war against opioid abuse. It's promoting prescriber and patient education on appropriate drug use, and agency scientists are working with academics on research methods for assessing opioid effectiveness and innovative package designs that may deter misuse.

Public officials also are taking action. New York City Mayor Michael Bloomburg announced in January that city emergency rooms would provide only three-day supplies of opioid painkillers to patients (3). Hospitals in Utah, Michigan, and Wisconsin are reducing or eliminating opioids from emergency rooms in favor of non-narcotic medications. Yet, a tough anti-abuse law in Kentucky is headed for revision because it created access problems for seriously ill patients.

State attorneys general (AGs) also weighed in recently, calling on FDA to require generics makers to produce tamper-resistant versions of opioid medicines. In a letter to commissioner Hamburg March 11, 2013, 48 AGs raised concerns that illegal users are shifting to older, more easily abused products as the newer formulations come to market (4). Regulation and production of dangerous, but clinically important, drugs is not simple from any perspective.

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Advancing QbD in the EU

The European Union authorities are stepping up their efforts to incorporate quality-by-design principles into their regulations and guidelines.

The European Commission (EC) and the European Medicines Agency (EMA), have been supporting quality-by-design (QbD) concepts over the past 10 years. In 2003, EMA set up a team to back activities in process analytical technology (PAT) in the EU. The agency has seen its PAT team as a key element in the implementation of QbD by encouraging process understanding. This knowledge becomes a basis for achieving quality by ensuring pre-defined quality criteria are met through design rather than *ad-hoc* testing. However, EMA has not been a strong driving force behind the adoption of QbD in the EU compared with FDA in the United States.

Greater recognition should be given to an enhanced QbD approach.

Recently, both EMA and the EC have experienced pressure from the pharmaceutical industry, particularly in the biopharmaceutical sector, to do more to encourage QbD. In addition, EU authorities are becoming more concerned about the increasing number of quality defects in pharmaceutical manufacturing that have been causing a rise in drug scarcities.

ICH guidelines

The industry has been wanting to see greater use of the Q8, Q9, and Q10 guidelines of the International Conference on Harmonization (ICH), which contain most of the basic QbD principles. These guidelines cover pharmaceutical development concepts in Q8, quality risk management (QRM) in Q9, and a pharmaceutical quality system to be implemented in the different stages of a product lifecycle in Q10. The ICH guidelines offer pharmaceutical manufacturers the option of taking the "minimal" or traditional approach to quality assurance or an "enhanced" structured approach, which involves concepts like critical quality attributes (CQA), design space, and control strategies.

The industry has been urging EU authorities to put more emphasis in regulations and guidelines on the enhanced attitude to quality, particularly because QbD is seen as a means for easing the regulatory burden with less need for inspections and post-approval submissions. EMA has, however, stressed that the adoption of an enhanced QbD approach by drug producers is optional rather than a requirement.

In comments published last year on proposed changes yet to be finalized to EU regulations on approval of manufacturing variations after marketing authorization, pharmaceutical trade associations called for more accommodation of elements of the ICH guidelines in the legislation. EuropaBio, which represents both biotechnology companies and national associations in Europe, said in its comments, published in July 2012 on a proposed revised guideline on variations, that greater recognition should be given to an enhanced QbD approach. This approach would provide opportunities for "a more science- and risk-based approach" in assessing manufacturing changes.

In a joint comment, the European Federation of Pharmaceutical Industries and Associations (EFPIA), representing original drug producers, European Biopharmaceutical Enterprises (EBE) and European Vaccine Manufacturers (EVM), urged the EC to make clear in legal text that changes within a design space did not constitute variations that need to be approved. Design space is defined as a QbD component that sets the combination of variables and process parameters providing assurance of quality.

The pharmaceutical industry in Europe sees QbD concepts as reflecting existing practices in the sector. Introducing them in regulations and guidelines gives more emphasis to the important elements in quality assurance.

"The adoption of ICH Q8–10 is not introducing new requirements or expectations," says Julie Marechal-Jamil, senior manager of quality and regulatory affairs at the European Generic Medicines Association (EGA), Brussels. "But the regulatory adoption of the guidelines is clarifying what elements are considered essential to support the pharmaceutical development section of a marketing authorization application dossier." Nonetheless, she claimed that "many practical questions regarding implementation of QbD remain open—even for medicines originators."

The European Commission's latest revision of its GMP guide, effective from Jan. 31, 2012, shows the degree to which it is responding to calls for ICH guidelines to be given greater prominence in EU rules on quality in pharmaceuticals. Chapter 1 of the guide has been changed to align it with the concepts and terminology of the ICH Q10 guideline on pharmaceutical quality systems. It makes clear that this new chapter will also apply to two existing pieces of EU legislation on the principles and guidelines of GMP—one, for medicines for human use, and other, for veterinary applications. References in the legislation to "an effective quality-assurance system" that manufacturers must establish and implement will now be taken to mean the ICH pharmaceutical quality system. "For the purposes of this chapter, these terms can be considered to be interchangeable," states the revised guide.

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Chapter 7 of the guide on outsourced activities has also been revised to take into account the ICH Q10 guideline. The biggest change in the GMP guide is a massive extension of Annex 2 on the manufacture of biological active substances, which has been extended from five to 32 pages and from 43 sub-items to 70.

"The enlargement has been necessitated by the introduction of new manufacturing technologies and the increased breadth of biological medicines into areas like gene and cell therapy," says the Commission. It is also because of the incorporation of components of the ICH guideline on QRM. "These biological principles may display inherent variability," the new annex states. "As a result, QRM principles are particularly important for this class of materials." The annex includes a new section on operating principles emphasizing the need for control strategies based on QRM principles to cover various key features of production processes.

The GMP guide may have to be further updated to highlight the importance of certain aspects of ICH guidelines because of what EMA describes as "public health crises" due to disruption to drug supplies caused by manufacturing problems. In a discussion paper issued in late 2012, the agency pinpointed the need for tighter controls on outsourced manufacturing to ensure that it is GMP compliant. EMA also thought that details of the "pre-planned inclusion of failsafe manufacturing site capacity" should possibly be included in marketing authorizations. In the longer term, the agency is considering making some QbD elements mandatory rather than optional by requiring submissions by all marketing authorization holders of risk analyses of their manufacturing processes to identify weaknesses.

Reducing drug shortages

EMA is also looking to collaborate with other licensing agencies outside Europe on ways to reduce drug scarcities, including the sharing of information about product-supply issues. EMA is already involved in a joint program with FDA on the parallel assessment of marketing authorization and new drug applications, which include QbD approaches.

One key objective of the three-year program, due to end in March next year, is to ensure consistency between the EU and the US in the implementation of ICH Q8, Q9, and Q10 guidelines. Assessments of applications are being done in parallel by the two agencies after which the review teams will discuss lessons to be learned and identify knowledge gaps. The pilot scheme should increase the momentum behind the uptake of QbD principles in Europe among both regulators and pharmaceutical manufacturers as well as lead to a more uniform policy between the EU and the US in the use of QbD to tackle issues like drug shortages due to production disruptions. **PT**

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is director of the European Directorate for the Quality of Medicines and Healthcare.

The Need for Pharmacopeial Harmonization

In the context of international trade, the need to develop global quality standards for medicines is increasing.

Quality standards are vital instruments in the context of marketing authorization and market surveillance, and they facilitate free movement and trade of medicines among countries and regions. The *European Pharmacopoeia* (*Ph. Eur.*) has always been at the forefront of the harmonization of quality standards. Indeed, almost 50 years ago, the "founding fathers" of the Convention on the elaboration of a European pharmacopoeia had already identified the need to harmonize quality requirements for medicinal products on the European market. They also acknowledged the difficulties in retrospective harmonization and so decided to begin establishing the *Ph. Eur.* by focusing on substances for which there were no existing standards in member states. The Convention was signed by eight countries in 1964 and, today has 38 signatory parties—37 states and the European Union.

The aim is to arrive at interchangeable methods or requirements.

The success of this pan-European undertaking and its impact on a global scale is demonstrated by the 24 observers to the Convention, comprised of 23 countries from all around the world and the World Health Organization (WHO). The positive experience gained in prospective harmonization and the trust and mutual confidence developed between participants in the early years has, in the meantime, also been translated into retrospective harmonization. Today, topics that are of interest to more than one member state end up on the work program of the European Pharmacopoeia Commission, regardless of whether or not a national standard already exists.

A changing industry

Since the establishment of the European Pharmacopoeia in the 1960s, the world, and with it the pharmaceutical industry, has changed significantly. International harmonization among the three pharmacopoeias of Europe, Japan, and the United States (i.e., the three regions that started the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH]) was, therefore, a logical development. Harmonization activities among the European, Japanese, and US pharmacopoeias began in 1989 with the establishment of the Pharmacopoeial Discussion Group (PDG); an informal harmonization initiative between these pharmacopoeias parallel to ICH. In fact, it was a prerequisite for the ICH Steering Committee to agree on the elaboration of the ICH Guideline Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products* that the PDG committed to harmonizing the 11 general methods referred to in the document at that time and not to make unilateral changes once harmonization was complete. The ICH Q6A guideline includes a specific reference to the work of the PDG in chapter 2.8 "Pharmacopoeial Tests and Acceptance Criteria."

Where harmonization of general chapters is carried out, the aim is to arrive at interchangeable methods or requirements so that demonstration of compliance using a general chapter from one of the three pharmacopeias implies that the same result would be obtained using the general chapter of any of the other two PDG pharmacopeias. However, the activities of the PDG in harmonizing general methods have not been limited to the Q6A methods; a wide range of general methods (35) has since been added to the work program. These include methods, such as chromatography, that are crucial for the quality control of medicines and a prerequisite for further harmonization of specific monographs. Besides the harmonization of general methods, the PDG has also been working on monographs for widely used excipients. Currently, 62 such excipients are included in its work program. Clearly, the purpose of harmonizing a monograph is to arrive at identical requirements for all attributes of the product in question.

To date, 28 of the 35 general methods and 43 of the 62 excipient monographs have been harmonized. Detailed information on the work program of the PDG is published in *Pharmeuropa* and the respective forums of the other two PDG pharmacopeias. In addition, the *Ph. Eur.* contains a specific General Chapter 5.8., Pharmacopoeial harmonization, that provides more information on the outcome of harmonization. This chapter was revised by the Ph.Eur. Commission in November 2012 to provide further support to users by highlighting information on any nonharmonized attributes/provisions and on any local requirements (i.e., attributes that are present only in the *Ph. Eur.* text). Non-harmonized attributes/provisions are placed between black diamonds (◆◆) in the corresponding *Ph. Eur.* texts, and the local requirements are marked by white diamonds (◊◊).

The PDG has often been criticized of slow progress. However, it has to be acknowledged that the three pharmacopeias have differing legal statuses; the Japanese Pharmacopoeia is part of the Japanese government's Ministry of Health, Labour and Welfare; the European Pharmacopoeia is part of the Council of Europe (an inter-governmental organization); while the US Pharmacopeia Convention (USP) is a private, not-for-profit organization that is independent

of the US government. In addition, all three are embedded in their specific national/regional regulatory frameworks that, after more than 20 years of activity at the ICH level, are only partially harmonized.

Harmonization of APIs

In addition to PDG activities, Ph. Eur. and USP have initiated a bilateral pilot project on the prospective harmonization of monographs for APIs. So far, this project covers four substances that were still under patent at the time monograph elaboration was initiated and it has been run in close collaboration with two sponsors. All four monographs have now been adopted by the respective governing bodies of the *Ph. Eur.* and *USP*. Together with the sponsors, the two pharmacopeias have decided to extend the pilot phase to cover the revisions of these first four monographs to ensure a robust procedure is in place before a final decision is taken on the future process. In the meantime, the Japanese Pharmacopeia has also voiced its interest in participating in the project.

Since the setting up of the PDG and ICH, the industrial environment has changed. It is evident that harmonization between the three ICH regions is no longer sufficient in today's world, where a high percentage of APIs come from outside Europe, Japan, and the US. Up to 80% of the volume of APIs used in the production of medicines for the European market come from India and China, with the cited figures varying depending on the source of data. The European Pharmacopoeia, therefore, is also actively involved in a number of other international harmonization projects; the most promising of which is the recent WHO initiative.

Good pharmacopeial practices

In early 2012, the WHO convened the pharmacopeias of the world for their first international meeting in Geneva. Representatives of 23 pharmacopeia secretariats from 21 countries, the EDQM/Council of Europe, and the WHO used the opportunity to exchange views on experiences, policies, and challenges. The discussions clearly identified the need to strengthen collaboration among pharmacopeias worldwide. Based on the experience and challenges with existing harmonization initiatives (such as the PDG) that focus on retrospective harmonization, it was acknowledged that new platforms open to all pharmacopeias who wished to participate would need to be identified for a global pharmacopeial harmonization process. However, any platform would need to respect that each pharmacopeia operates within a national or regional legal and regulatory

framework. Hence, the main emerging proposal has been the development of *Good Pharmacopeial Practices*; a guidance document that would describe harmonized policies and approaches to monograph development, collaboration between pharmacopoeias, and interactions with stakeholders. Good pharmacopeial practices are intended to favor and facilitate future collaboration, work-sharing, and prospective harmonization between participating pharmacopeias.

The WHO has been asked to facilitate the elaboration of these good pharmacopeial practices under the auspices of its Expert Committee on Specifications. An initial drafting group has been formed, comprising representatives from Argentina, Brazil, the Ph.Eur., India, Japan, Mexico, Russian Federation, Ukraine, and USP, with editorial assistance being provided by the United Kingdom. As a truly global initiative, the entire process will be open to all pharmacopeias. A follow-up meeting, organized jointly by the WHO and the Fédération Internationale Pharmaceutique (FIP) in October 2012 in Amsterdam, gave the opportunity to the pharmacopeias to present this proposal to stakeholders and to collect feedback. As a consequence of this discussion, a second closed international meeting of world pharmacopeias is now planned to take place in India in April 2013, hosted by the Indian Pharmacopoeia Commission and co-organized with the WHO.

The WHO has been asked to facilitate the elaboration of these good pharmacopeial practices under the auspices of its Expert Committee on Specifications.

Preparation of a first draft of the *Good Pharmacopoeial Practices* guidance document as a basis for substantial discussions and progress at this meeting is well under way, with pharmacopeias from different continents sharing the work. The Ph. Eur. Commission supports these developments, which will help the pharmacopeias of the world to agree on harmonized, scientifically sound approaches and policies to ensure the quality of medicines for the benefit of patients around the world. **PT**

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Desmond Hunt, PhD,
is a senior scientific liaison at USP.

Moisture Permeation of Pharmaceutical Packaging

USP is proposing a new performance testing standard for moisture permeation of pharmaceutical packaging.

A key factor in maintaining the quality of a pharmaceutical product throughout its shelf life is the integrity of its packaging. Preventing moisture from permeating through the packaging is an important function of the container-closure system used for medicines. Today, moisture uptake is a common cause of product package failures in the pharmaceutical industry—and a topic that the US Pharmacopeial Convention (USP) is addressing with an upcoming revision to *United States Pharmacopeia–National Formulary* (*USP–NF*) General Chapter <671> Containers—Performance Testing for Plastic Containers.

An underlying issue relevant to this activity is the USP classification system for packaging.

Updating General Chapter <671>

Initially developed in the 1970s primarily for use by pharmacists dispensing medications into the familiar amber vial, General Chapter <671> has become heavily relied upon over the years by pharmaceutical manufacturers, packagers, repackagers, and FDA because it is referenced in the agency's *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics*. However, the general chapter has had only minor edits and additions in intervening years. Because it is being used beyond its original scope and utilizes an older permeation test, modifications to the general chapter have become necessary. This effort is supported by industry, and the newly proposed standard builds on method development work completed over the past decade by the Product Quality Research Institute (PQRI). PQRI is a nonprofit consortium of organizations that conducts research to generate specific scientific information on issues of interest to FDA and to standards-setting organizations such as USP.

One of the key ways the general chapter is being updated is through the proposal for a new moisture vapor transmission rate test method for solid oral-dosage forms. The current test method is a gravimetric method that is not very robust, which can lead to variation in test results. The proposed new method is also gravimetric, but is more reproducible and uses more rigorous environmental test conditions. Both the older and newly proposed methods measure weight gain over time. However, the information yielded by the new method will give end-users a more accurate assessment of how much protection their packaging is affording to the final product.

ASTM standard

The proposed general chapter, including the new method for calculating moisture vapor transition rate, aligns with the recently released ASTM International standard: "ASTM D7709–12 Standard Test Methods for Measuring Water Vapor Transmission Rate (WVTR) of Pharmaceutical Bottles and Blisters." ASTM sets international voluntary consensus standards. The revised USP general chapter is included in *Pharmacopeial Forum* 39(2) March–April 2013, and USP invites comment on the proposal at www.usp.org/usp-nf/pharmacopeial-forum.

Classification

An underlying issue relevant to this activity is the USP classification system for packaging. At present, USP specifies the categories of "well-closed" and "tight" in its classification, with the latter used much more frequently. Certain medications, however, require packaging beyond "tight"—requiring no moisture permeation. While no change to the classification system was included in the new proposal, USP would like to open a dialogue with regulators, manufacturers, contract packagers and repackagers, and other stakeholders about whether, and how, this classification system could be expanded. The classification system—along with applications of the new <671> method, manufacturer case studies, current regulatory thinking from FDA, and other areas affected by the new method (e.g., desiccant choice, which is particularly important with the method change)—will be among the important areas of discussion at a May 20–21, 2013, workshop cosponsored by USP and PQRI in Rockville, MD. More information about this workshop is available at www.usp.org/meetings-courses/workshops/pharmaceutical-packaging-moisture-permeation. **PT**

See page 102 in this issue for USP's review of "Fixed-Oil Excipient Monographs."

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Trends in GMP Violations

FDA's Brian Hasselbalch provides an overview of trends found in FDA quality inspections over the past year.

It is essential that pharmaceutical manufacturers follow current good manufacturing practices (CGMPs) to ensure product quality and patient safety. FDA regularly inspects the manufacturing facilities of pharmaceutical companies to determine if GMPs are being followed. *Pharmaceutical Technology* spoke with Brian Hasselbalch, Acting Associate Director for Policy and Communication, Office of Manufacturing & Product Quality, Office of Compliance at FDA's Center for Drug Evaluation and Research, to find out what trends in GMP violations and quality issues the agency has discovered in the past year.

Top GMP deficiencies

PharmTech: What were some of the top GMP deficiencies in pharmaceutical manufacturing that FDA documented in 2012?

Hasselbalch (FDA): FDA inspections of drug manufacturers are designed to always evaluate the facility's quality system. The quality system includes evaluation of manufacturing problems—complaints, recalls, deviations, defects, and failures—so it may not be surprising that we tend to find CGMP deficiencies in this area. Inspection findings from 2012 show CGMP deficiencies in the following major areas:

- The quality unit does not function as the CGMP regulations require: Approving or rejecting procedures, major decisions about quality including batch release (21 *CFR* 211.22).
- Production and process controls are not proven valid and/or are not in writing sufficient to assure consistent performance (21 *CFR* 211.100).
- Complaints, defects, and failures are not fully investigated to determine cause and/or full scope of impact (21 *CFR* 211.192).
- Facility and equipment are not designed or maintained to assure cleanliness (sanitary surfaces and/or free of residual drug contamination) (21 *CFR* 211.67).

Major trends

PharmTech: What were the major trends in quality control violations in pharmaceutical manufacturing?

Hasselbalch (FDA): There is a problem of oversight: the quality unit is not governing operations as required; management is not providing sufficient resources to quality assurance activities. In some cases, we see evidence that the quality unit is not being allowed to govern operations bearing on quality assurance, and batch release decisions are made contrary to the CGMP regulations.

One area of change from past years to the more recent full year is that facility cleaning and equipment maintenance deficiencies have increased. FDA Warning Letters over the same period reveal problems particularly in sterile manufacturing operations, where the consequence of poor maintenance and cleaning often leads to more severe consequences for patient safety, such as production of a non-sterile injectable.

Improvements in quality control

PharmTech: What areas of quality control could pharmaceutical manufacturers improve upon?

Hasselbalch (FDA): First, manufacturers should prevent problems from happening by providing sufficient resources toward the creation of a well-designed, optimized manufacturing and control operation. This may not be a novel concept, but is still worth saying. Second, manufacturers should react more aggressively on information bearing on product quality. All too often, we see potentially negative quality information—such as consumer complaints, aberrant stability results, abnormal yield variations, adverse-event reports—being evaluated too slowly and incompletely. We understand the need for a response to such information to be thoughtful, but we often see manufacturers summarily disregard such data.

PharmTech: What areas have pharmaceutical companies improved upon in the past two years?

Hasselbalch (FDA): Inspection deficiencies appear to have decreased in quality-unit responsibilities (while still being higher than other types of deficiencies) and employee training.

Domestic versus offshore

PharmTech: What domestic manufacturing GMP deficiencies have FDA documented compared with offshore manufacturers?

Hasselbalch (FDA): Domestic and offshore manufacturers tend to have similar problems; usually, given the greater number of APIs being made offshore than here in the US, the differences are often explained by the nature of the processing and standards expected.

In fiscal year (FY) 2012, FDA performed approximately 500 preapproval-type inspections (specific to a site and application), which includes all types of application-listed facilities (API, finished product, processing, testing, and packaging). This is about the same number as in FY 2011.

In FY 2012, FDA performed about 1900 CGMP-type inspections (i.e., routine coverage) of facilities connected with human drug manufacturing (except medical gas; including all other drug types and APIs as well as finished product) here in the US and offshore. This is about the same amount as in FY 2011, but with one big difference: routine CGMP inspections of offshore facilities increased by about 20% in FY 2012 over FY 2011. We have planned for this increase to continue in FY 2013. Other FY 2013 changes over previous years include increased inspections of positron emission tomography facilities, which are primarily domestic sites. **PT**

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EMERGING MARKET REPORT

Report from: Thailand

Jane Wan

The Thai government is ramping up efforts to promote and develop the biotechnology sector in a bid to enhance its global competitiveness.

Thailand's biotechnology sector was given a boost when the drafting committee for the National Social and Economic Development Plan No. 11 decided to include it as part of the national plan for 2012 to 2016. The initiative received strong support from researchers, scholars, and related sectors considering the slow development of the biotech sector in Thailand, and also because such technology development will contribute to the country's economic growth.

Thailand's forte is in agriculture and food biotech followed by medical technology, says Hannah Nawi, associate director for healthcare of Frost and Sullivan. Seventy percent of R&D expenditure is being channeled to agricultural biotechnology. According to Nawi, the average export of agricultural and food products is valued at $23 billion.

Slow growth in biotechnology

The development of the biotech sector has, however, been slow in Thailand compared to Singapore and Malaysia. Last November, Malaysia attracted a total of $4.2 billion in biotech investment, exceeding the $2.9-billion target for its Phase II plan under the National Biotechnology Policy. Phase II focuses on biotechnology sub-sectors including drug discovery, new product development, technology acquisition, and licensing. Malaysia has consequently raised its 2015 investment target to US$8.5 billion. Singapore's biomedical sector, on the other hand, is already accounting for 5% of its economy. In 2010 alone, the country generated $7.5 billion compared to Thailand's $167 million.

"Thailand's biotechnology sector is hampered by the lack of scientific professionals, technological skills, and government support, although it appears that there is a strategic framework in place. Moreover, the key downside risk to biotechnology investment is the long incubation period. The risk of failure is high and investors' confidence is typically tied to the probability of success," commented Cher Boon Piang, analyst of Business Monitor International (Asia). Nevertheless, the current outlook has not discouraged the Thai government from increasing its support and involvement in the sector.

Over the years, agencies such as Thailand Board of Investment (BOI) and National Center for Genetic Engineering and Biotechnology (BIOTEC) have been playing a proactive role in developing Thailand's biotech sector. When BOI started promoting biotechnology in 2007, it came up with an eight-year corporate tax exemption and tariffs waiver on imported machinery. It also granted incentives to projects. In 2008, eight new projects worth $9 million received the thumbs-up for such benefits.

BIOTEC, on the other hand, channelled approximately $21 million to R&D activities in 2011. It collaborated with Novartis on a project to investigate the potential use of microorganisms and natural compounds as sources of new medicines to treat diseases such as cancer and tropical illnesses. Besides that, it assisted the Thai-based environmental and research company, Hi-Grimm, to launch KEEEN in 2010. KEEEN is an environmentally friendly bioremediation agent that uses microorganisms to eliminate hydrocarbons, fats, grease, and organic substances from contaminated areas. Hi-Grimm is currently producing and commercializing the final product.

Investing in biotechnology

Thailand is also building up its talent base, which is necessary for the sector's growth. On a yearly basis, it is producing 800 to 900 undergraduates pursuing a biotech degree, 300 to 400 individuals with Master's degrees, and 50 with doctorates across its 24 universities. Key statistics from BIOTEC show that of the 570 workers employed in the biotech sector, 539 are graduates, or postgraduates, and 472 are R&D scientific staffs. From a business perspective, Thailand has approximately 200 biotech companies

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in operation to date and the doors are opened for multinational companies to acquire or license Thai-based technologies. The Thailand Science Park, a world-class facility, houses more than 1600 full-time researchers. Its attractive features include long-term land leases for construction and ready-made wet laboratories for rent.

In February 2012, the Thai minister of public health expressed support for the Government Pharmaceutical Organization who is in the process of building a manufacturing facility for biotech and non-biotech products. Helen Featherstone, general manager of IMS Health Thailand, says: "In my opinion, Thailand's biotech sector will only start to develop within the next 10 years. Since the supply of these products will remain within the country's perimeters, foreign companies are likely to continue importing biotech products from other countries. On the other hand, local players are facing issues including governmental policy changes, increases in minimum wage, and pressure on pricing."

All is not lost for Thailand's biotech sector, although it is not likely to compete with Singapore and Malaysia given its current developmental stage. Cher says, "Thailand should find some niche sub-sectors to invest in. It has seen some success in microbial-based research so far and should look further into it given the high burden of tropical diseases in the country and its neighboring ones including Myanmar, Cambodia, and Vietnam."

Nawi adds, "Further development of the medical biotech sector lies in the country's competitive edge as a provider of clinical trials. Thailand offers fast patient enrollment with lower dropout rates, higher patient concentration per trial site, and a less expensive workforce to conduct the trials. It also has a well-developed hospital system to conduct the trials. Looking forward, we are likely to see interesting changes and developments in the coming years. But the government has to ensure that conductive policies and regulations are implemented to support the potential growth of the country." **PT**

—Jane Wan is a freelance writer based in Singapore.

IMPORTANT FACTS

- Under Thailand's first National Biotechnology Policy Framework (2004 to 2009), 90 new companies were formed, bringing the number of biotech companies to an estimated total of 170.
- Thailand has succeeded in producing the world's first commercial biosensor for avian influenza. Currently, it is in the process of producing its first indigenous drug to treat malaria. If successful, it will be a breakthrough development that puts Thailand on the world map.
- Thailand is regarded as a prime "pharmerging market" due to the potential of its biotech sector. The large population and academic/healthcare infrastructure make the country an ideal provider of clinical trials.

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EMERGING MARKET REPORT

Report from: Russia

Vadim Konyushkevich and Ksenia Stepanischeva

Strengthening government control or striving for compliance with international standards?

The Russian pharmaceutical market has been extensively developing over the past decade, largely influenced by foreign investments in this area of the country's economy. It is currently one of the top 10 largest pharmaceutical markets in the world. At the same time, the Russian pharma market has witnessed stricter state regulation of pharmaceutical activity, generally defined as a certain restraining measure over uncontrolled pharma market growth. The escalation of state control within the industry has been especially noticeable during the past two years.

A major factor influencing the Russian pharma market is the initiative to bring its regulation to compliance with international standards. Many experts link this initiative to Russia joining the World Trade Organization (WTO) on Aug. 22, 2012. This date has marked yet another stage of Russia's integration into the world economy and as of that day, Russia has become a full member of WTO. Consequently, there has been extensive changes in legal regulation for the pharmaceutical industry in 2012, namely in the areas of technical regulation, customs law, licensing requirements, relations of pharmaceutical companies with medical officials, competition, and advertising law.

Customs

Customs regulations for pharmaceutical drug import will change now that Russia has become part of WTO. In accordance with WTO's protocol on accession import customs, duty rates for drugs will gradually decrease from the current 10–15% to 5–6.5%; however, the process is long term and will not be completed until 2016. This gradual reduction of import duties for foreign drugs will not likely induce a noticeable price decline for end customers because the final cost will depend on the distributors as well as pharmacy extra charges. However, it is possible that there will be a reduction in price for expensive drugs, and Russian drug manufacturers are afraid that their market position may be weakened as a result of the decrease in price of imported medicines. Also, by joining WTO, Russian drugs can gain access into the international market due to the uniform rules followed by other WTO members in relation to Russian pharmaceutical products.

Eliminating discrepancy

Russia's WTO membership is also associated with obligatory implementation of international GMP standards in drugs manufacturing. The legal development in this area has not been extensive in 2012, but because of the necessity to bring drug quality in accordance with international standards, work on amending statutory basis in this field was initiated long before Russia's accession to WTO. Rules on manufacturing and control of drug quality, made on the basis of EU GMP, were enforced on Jan. 1, 2010. International standards for the manufacture of drugs will be gradually implemented through the transition period of Russia entering WTO. The production of drugs in compliance with international standards has already begun and its completion is planned at the end of 2013.

Escalation of state control

Governmental control (i.e., stricter governmental industry internal regulations) remains a significant trend that relates to the new licensing requirements, more specified regulation of

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drug manufacturing, registration, relations between medical and pharmaceutical employees, and provisions for advertising of medicines and medical products. Firstly, tightening of licensing requirements should be noted. On Jan. 1, 2012, a new Decree on the licensing of pharmaceutical activity came into effect, which introduced a detailed list of licensable activities as well as new requirements for licensing drug transportation (1, 2).

New rules on information disclosure in the course of clinical studies of medicines have been established as amendments in the federal law on "circulation of drugs" (3). The rule sets forth nondisclosure without prior consent of the results of preclinical and clinical studies provided for medicines registration. It is proclaimed to divulge any of this information within six years since the date of registration. Violation of this regulation incurs administrative and penal liabilities.

Regulating relations of medical officials

The year 2012 has also signalized a strengthening of regulation in the area of medical and pharmaceutical employees' relations. In particular, from January 2012, new wording of the federal law on "fundamental healthcare principles in the Russian Federation" (Law No. 323-FZ) has been enforced (4). Article 74 of this law sets a number of restrictions on the relations of medical officials with representatives of pharmaceutical organizations.

The policy amendment is that medical officials cannot receive any gifts or money from pharmaceutical organizations apart from consideration for agreements relating to clinical trials or implementation of educational activity. Healthcare professionals and pharmaceutical representatives cannot receive any gifts from the manufacturing company or pass drug samples to patients. In addition, it is prohibited to give out prescriptions on prescription forms containing any kind of advertising information or typed-in names of medicines. Doctors can only admit representatives of pharmaceutical companies, manufacturers or sellers of medicines in connection with the conduct of clinical trials or qualification trainings of medical officers. Any form of agreements that involve proposing certain categories of drugs or medical products to patients must be proclaimed. Further amendments are currently under review to introduce even stricter administrative liability for violations of abovementioned provisions.

New public control procedure

One of the latest developments in the Russian pharma legislation is the adoption of new government control procedures over medicines. On Nov. 12, 2012, Decree No. 1152 of the government of the Russian Federation affirmed regulations on quality and security of public control procedures over medical activity. These regulations provide more details on the means of public control over the industry.

Public control is to be conducted by means of scheduled routine inspections and random check-ups and/or on-site audit. A list of control measures has been set out for each kind of inspection taking place within the framework of public control relating to the quality and safety of the medical activity. These regulations provide for extreme forms of state control such as rights for official representatives to have full and unimpeded access to the territory or premises of the organizations under inspection, including the equipment and vehicles used. Representatives will also be able to copy any documents deemed to be necessary, conduct trials and examination, as well as apply precautionary and restrictive measures.

FAS against deemed violation of competition legislation

The Federal Antimonopoly Service (FAS) in association with the Ministry of Health of the Russian Federation developed in October 2012 a new draft of governmental regulations in accordance with provisions of the federal law on "allocation of orders for supply of goods, execution of works, and rendering of

contin. on page 137

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EMERGING MARKET REPORT

Report from: Latin America

Jill E. Sackman

Latin America's diverse growing market seeks regulatory harmonization.

Latin America is one of the top emerging markets in the bio/pharmaceutical industry. This region shows a great deal of diversity in its approach to pharmaceutical products as a result of differences in economics, resources, access to care, and definition of regulatory requirements by country. Common guidelines from groups like the Pan American Health Organization (PAHO), part of the World Health Organization (WHO), and the Mercado Común del Sur (Mercosur), a lead trade organization, are just beginning to be implemented. There's interest in greater harmonization, like Eastern Europe, across the region, but there still remains great divergence between individual countries.

With its population reaching 600 million people in 2011, Latin America is a fast growing region with equally fast growing economies. The top four Latin American economies and pharmaceutical markets account for more than 60% of the total population: Brazil (194 million), Mexico (115 million), Colombia (46 million), and Argentina (41 million). Other major players include Chile, Peru, and Venezuela (1).

Latin American pharmaceutical sales in 2011 were at $62.9 billion, registering 8.9% growth in 2012. This is particularly significant when considered within the context of global sales of $995 billion in 2011. The diversity of the region, however, presents some challenges. In addition to the fact that guidelines from PAHO and Mercosur are just beginning to be implemented, it's also worth noting that what exists are just guidelines, subject to regional and country specific variations. Other differences (e.g., economic differences, population differences, political differences) have profound implications for the pharmaceutical marketplace in Latin America.

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Key regulatory considerations

The primary regulatory consideration across the Latin American region for pharmaceutical companies is the increasing trend toward standardized regulations. Each of the seven major markets has adopted regulations that are based on Mercosur or PAHO's recommendations. For example, Brazil revised its GMP standards in 2010 to ensure greater consistency with Mercosur/PAHO recommendations. Updates to Brazil's GMPs addressed the areas of quality, sanitation, hygiene, qualification and validation, contracts, and computer system validation. Since then, Brazil has been moving ahead with implementation, including the release of a guidebook for inspections in May 2012.

In other cases, such as Mexico, international agreements like the North American Free Trade Agreement protect foreign companies interested in expanding their business into the region. The Mexican federal commission for sanitary risk (COFEPRIS) also holds equivalence agreements with Health Canada and FDA for the regulation of drugs and medical devices. Additionally, in September 2012, COFEPRIS and the Chilean Public Health Institute signed a cooperation agreement that will allow for the harmonization of regulatory requirements within the Americas region, breaking the entry barrier present in many countries. The agreement, which is still at the "memorandum of understanding" (MOU) stage, is a bilateral mechanism that is eventually expected to allow the mutual recognition of marketing authorizations, inspection visits, and GMP certification. Mexico has also signed

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other equivalence MOUs with El Salvador and Ecuador, and a MOU is in the making with Colombia. MOUs with Brazil and Argentina are expected in the near future.

Even with all of these agreements, there is no Latin American equivalent of the European Medicines Agency—no common body with the power to facilitate greater consistency across countries. Mercosur and PAHO can make recommendations, but cannot enforce a common set of rules the way a common governing body can. And to complicate matters, even as countries implement regulations to be more aligned with Mercosur and PAHO recommendations, they may not implement the same regulations at the same time.

Despite the many efforts carried out by the major Latin American markets, the road toward total harmonization is steep. The main reasons are the size of the region and the number of countries included in the area, each of them with their own regulatory system, political background, and policy approach to healthcare and pharmaceuticals. One proposal has been that of convergence rather than harmonization similar to what is in use in the Asia Pacific Economic Cooperation Area (APEC). Regulatory convergence is a voluntary process in which the countries in question agree to work toward regulatory requirements that are similar, but not fully harmonized. Harmonization would require changing laws in each country and is, therefore, more difficult to achieve. Convergence of regulations is considered as the most viable solution for the Latin American region.

Other considerations for pharmaceutical companies interested in expanding in Latin America include regulatory risk profile. In general, Latin American pharmacovigilance systems have developed considerably since the early 1990s and continue to strengthen. Several countries have set up adverse events reporting systems for products in the market, and 10 countries have regulations reporting adverse events during clinical trials.

Countries that currently have low pharmacovigilance requirement levels must still develop a system and appropriate monitoring measures. They are strongly encouraged by the WHO to do so in a timely fashion. The Subregional Pharmacovigilance Programmme and the Pan American Network for Drug Regulatory Harmonization also assist countries in Latin America in developing pharmacovigilance regulations that are harmonized with other Latin American countries.

Product reimbursement

The way that payment is structured varies tremendously. For example, in Mexico, the government pays for approximately 45% of healthcare—significantly less than other Latin American countries. Other markets in the region, particularly Venezuela and Chile, have implemented Latin American social medicine (LASM) practices. In Venezuela, these practices have manifested as Mission Barrio Adentro, a national social welfare program comprised of neighborhood healthcare clinics built in the past decade intended to provide universal primary care to Venezuelans. Though both WHO

and UNICEF have praised the program for its holistic approach to community health, critics have argued that building the planned 8500 local clinics siphons resources away from traditional hospitals.

It's crucial that pharmaceutical companies understand how healthcare is delivered in each Latin American market, because there is such a degree of diversity. How payment is structured and care is delivered impact the number of stakeholders to whom companies have to present the case for their products.

Key market considerations

Beyond understanding the regulatory landscape of each market, there are other market characteristics to consider as well. For example, in some markets like Argentina, the majority of pharmaceutical sales are currently going to domestic companies. Chile, on the other hand, only produces a small amount of medical equipment locally, though some protectionist regulation meant to encourage local industry complicates the landscape for companies looking to expand there. Some countries, such as Colombia, produce pharmaceuticals that are imported by other countries in the region, especially Venezuela.

Beyond the current makeup of the pharmaceutical industry in each nation, understanding the demographics and political landscape of each market is essential. Chile, for example, while smaller in market size than Brazil or Argentina, has the highest gross domestic product (GDP) per capita in Latin America. In May 2010, Chile became the first South American country to join the Organisation for Economic Co-operation and Development (OECD).

The Mexican market offers some other demographics that make it attractive for healthcare. The population has continued to grow by nearly 9% between 2005 and 2010, at the same time that life expectancy also increased. In addition, the Mexican government has, in the past decade, launched programs aimed at expanding health insurance. In 2003, the government started *Seguro Popular*, which offered publicly provided health insurance to some poor families. In the years since, Mexico has launched other initiatives, including Medical Insurance for a New Generation aimed at disadvantaged children under the age of five, and Universal Care Coverage for Pregnant Women in 2009. Health spending is still lower than the OECD average, but coverage has increased.

The existing infrastructure must be kept in consideration. Mexico has a considerable manufacturing industry, but its research and development sector is less developed. Mexico spent $6.4 billion, or 0.4% of its GDP, in R&D across all sectors in 2011. As a percentage of GDP, this is less than half as much as Brazil spent the same year, and less than a quarter of the OECD average (2, 3).

Implications for successful market entry

Latin America clearly offers substantial

business opportunities for pharmaceutical companies. The region represents a growing consumer base for the drug industry; by 2020 the regional population is projected to be as high as 687 million. The Latin American pharmaceutical market is now worth $45 billion and multinational companies consider success in Brazil and Mexico as essential. Some of the main challenges and opportunities in the region include:

- Intellectual property. Legal oversight of intellectual property is often weak or not enforced in a number of Latin American countries.
- Generics. Regional governments are making serious attempts to encourage the use of generics. This push may be a significant opportunity for pharmaceutical manufacturers with generic portfolios.
- Clinical trials and R&D. Com-panies are finding Latin America attractive for R&D and clinical development. There are currently an estimated 4000 clinical trials being conducted. High enrollment rates, lower labor costs, and improving regulation have encouraged growth in outsourcing. Modernization of local regulatory guidelines is ensuring faster project start-up and shorter clinical trial approval times. There is also a strong knowledge and practice of International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines and western medicine standards.
- Political situation. Unsettling for multinational companies is the political shift to the left in some countries. However, a number of countries are working to introduce universal healthcare coverage that could create excellent long-term opportunities. Despite the political situation, many governments are highly motivated to make the region favorable for clinical studies and R&D.

Moving Forward in Latin America

As a developing market, Latin America is quite complicated and diverse in terms of regulatory, reimbursement, market, demographic, and political characteristics. As regulatory trends converge and the market continues to grow, the region represents a substantial opportunity for pharmaceutical companies, especially those that take the time to understand these characteristics and anticipate the direction each market will take.

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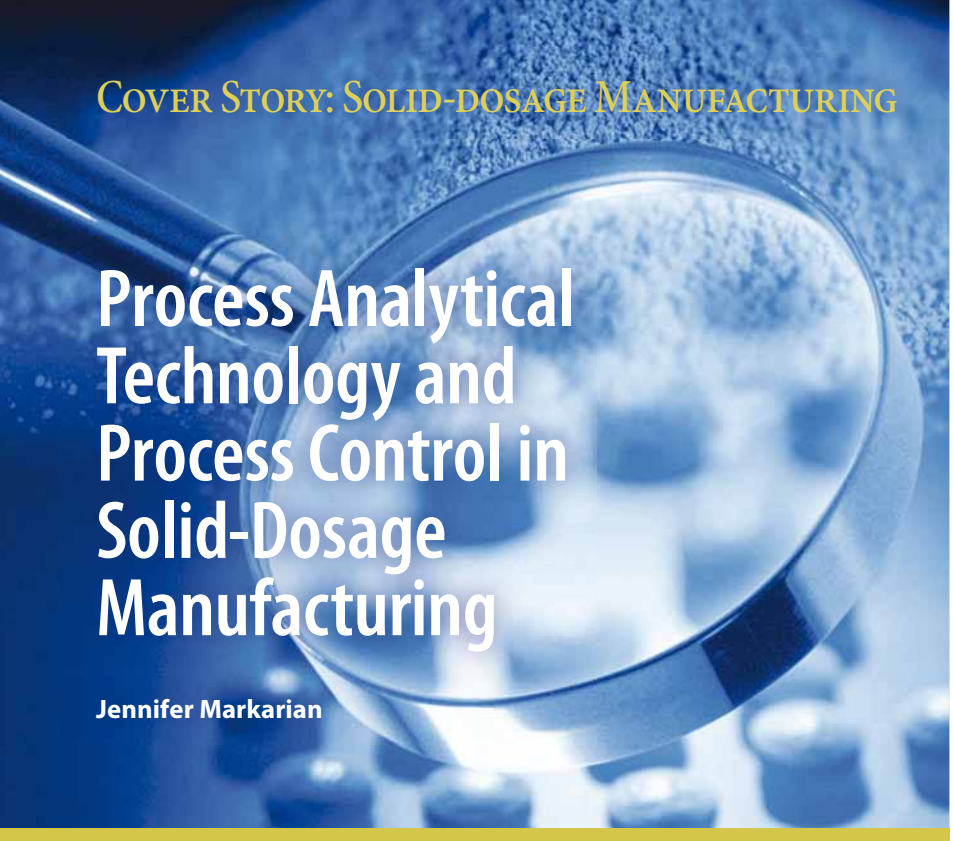

Process Analytical Technology and Process Control in Solid-Dosage Manufacturing

Jennifer Markarian

Industry is moving toward closed-loop control of continuous processing.

Since FDA issued its report, *Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century—A Risk-Based Approach* (1), and its guidance on process analytical technology (PAT) (2) in 2004, academia and industry have been making strides in integrating quality-by-design (QbD) principles and PAT into solid-dosage manufacturing processes.

PAT and QbD principles both emphasize the need for process and material understanding as a basis for effective control of the process. "This emphasis has stimulated the industry to focus on how to get the information it really needs, which is leading to a productive re-examination of the existing analytical toolkit and an embracing of newer technologies that deliver the goods," says Tim Freeman, managing director for Freeman Technology. Progress has also been made in integrating PAT into continuous manufacturing of finished-drug products, with the eventual goals of closed-loop control and real-time product release.

PAT

Online PAT is successfully being used to optimize individual unit operations in solid-dosage manufacturing by monitoring on-line critical quality attributes (CQAs). Data from PAT give manufacturers better understanding and can be used to control the unit operation. Moisture content, for example, is used to determine the endpoint of a drying cycle. In tableting, the most common online measurements are near infrared (NIR) spectroscopy, which measures moisture content and blend uniformity, and laser-diffraction particle sizing.

Bulk-powder characterization techniques, which are performed at-line or in the laboratory, also fulfill the purpose of PAT by providing crucial information in a timely manner. "Precisely quantifying the flow behavior of powders, either as raw materials or as a blend, and other characteristics such as the ease with which a powder entrains and releases air, supports the development of more efficient processes," explains Freeman. Flow-property measurements are increasingly being recognized as a desirable online measurement, but this technology is not yet available.

Continuous solid-dosage manufacturing

PAT can be used in continuous solid-dosage manufacturing, in which individual batch-processing units are connected in one process train. Advantages of continuous manufacturing include a smaller equipment footprint, production volume flexibility, and higher production efficiency, in addition to the potential for improved quality and process stability as a result of employing PAT. Continuous processing also allows more efficient process development. Because parameter-change effects can be measured in nearly real-time using a continuous setup, dozens of conditions can be tested in hours rather than days or weeks, notes Douglas Hausner, associate director for industrial relations and business development at the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), which is based at Rutgers, the State University of New Jersey. In most cases, the same equipment used in the development stage can be used in production, which eliminates the need for scale-up.

Although most solid-dosage processes today operate as a series of independent unit operations, pilot programs for continuous processing have made progress, and commercial implementation could occur within the coming year. The design of a continuous direct-compaction line built at C-SOPS, for example, was recently used to construct a commercial line at Janssen, which will be filed for FDA approval.

GEA Pharma System's ConsiGma continuous manufacturing platform is an example of a commercially available continuous-manufacturing system. It can incorporate several different continuous technologies for the production of solid-dosage forms, such as wet granulation, dry granulation, and direct compression. The ConsiGma wet-granulation line consists of a blender, twin-screw granulator, fluid-bed dryer, granule conditioning unit, rotary tablet press, and continuous coater. This new generation of continuous manufacturing technology minimizes start-up and shut-down material losses because steady state can be reached quickly, notes Kris Schoeters, product manager for continuous processing at GEA Pharma Systems. PAT plays a crucial role in the GEA system. In the granulator, online optical systems are used to measure CQAs. Moisture content and blend uniformity are measured using NIR. Particle size is measured using an online laser-diffraction system,

and tablet-content uniformity is measured using Fourier Transform (FT)-NIR transmission spectroscopy. Measurement data feeds into a process-control system to reach the goal of closed-loop control.

Sampling challenges

Incorporating PAT into a continuous process for solid-dosage drug production has not been a simple task, however. One challenge has been retrofitting the equipment to enable collection of the correct data from PAT devices. Some measurements (e.g., flow, pressure, and temperature) are readily available from inline sensors. Other measurements, such as online NIR spectrometry, are more complex and have required creativity in the physical interface with processing equipment. Enabling the sensor to collect good data, for example, has often required that probes and windows be retrospectively engineered into the processing equipment.

"NIR is a reflectance measurement that measures whatever is sampled by the probe. If a sample is stuck to the probe lens, it will be measured repeatedly," notes Hausner. The C-SOPS line incorporates a window for the NIR measurement in the transfer pipe directly above the tablet press to measure blend content as close as possible to the tablet press. C-SOPS researchers investigated several different designs of modifying the pipe leading into the tablet press. The researchers concluded that plug-flow without turbulence was crucial to minimizing noise and allowing the analysis to run quickly.

GEA Pharma's self-cleaning Lighthouse Probe, developed with J&M Analytik, was designed as a solution to the problem of sample adhering to the lens (see **Figure 1**). The viewing windows can be cleaned during the process, and a self-calibration feature indicates if a window is contaminated.

Work at Pfizer included developing solutions for sampling, such as screw transfer devices that enable sampling points to be inserted in flowing powders and developing heated probes to avoid material sticking, notes Steve Hammond, senior director and team leader of Pfizer's Process Analytical Sciences Group. Pfizer also conducted experiments to determine reflective properties of powders, depth of

Figure 1: An in-process optical probe enables process analytical technology (Lighthouse Probe, GEA Pharma Systems).

FIGURES ARE COURTESY OF GEA PHARMA SYSTEMS

penetration, and return of radiation in loose and compressed powders. Other aspects of sampling, such as mass of material contributing to a measurement, integration times for scanning, and the effect of reference scanning had to be extensively studied and understood, adds Hammond.

Integrating PAT and process control

The next step after integrating PAT into the continuous process as a monitoring tool is to incorporate the data from PAT into process control. In a feed-forward/feed-backward or closed-loop control system, critical process parameters (CPPs) are dynamically adapted and fed to the controller to keep the process within specification. In today's batch processes, unit operations are operated as "islands of automation," but the goal of continuous processing is to control multiple, single units as one unit by using an overarching process-control system.

Closed-loop control has been used successfully for many years in other process industries. "The frightening part for the pharmaceutical industry is moving from manual control with people making decisions to advanced process control, in which process data and modeling software automatically control the process," comments Jonathon Thompson, senior manager of Compliance Services Consulting at Invensys. "PAT can give you a lot of data, which you need to turn into information about the process and whether it is within the CQA parameters," he explains. "Process-modeling software compares real-time data to an ideal or 'golden' batch profile, identifies what parameters need to be changed to meet the ideal, and feeds this back into the control system."

Researchers have been addressing several issues while integrating process control. One issue is that although some process equipment (e.g., newer feeders) is typically already instrumented for control, other equipment may require retrofitting. The tubular blender used at C-SOPS, for example, had a simple motor with a tachometer to control the speed, and C-SOPS engineers added instrumentation to allow more sophisticated control of the blender speed.

Integration of instrument software with plant equipment is a challenge. Some installations that require simple endpoint or on/off control could use simple, analog 4–20 mA connections, says Hammond, but the most valuable applications generally require more sophisticated control that involves developing either direct communication with the manufacturing equipment's control systems or communication with plant supervisory control and data acquisition (SCADA) systems.

"Ten years ago these communication links were custom developed for each piece of equipment. In recent years the development of "open architecture" software has simplified this aspect of instrument integration," explains Hammond. Open-architecture software (e.g., OPC) uses open standards that enable connectivity. This software meets the need for communication protocols to enable analytical instruments to communicate with control

systems, says Hammond, who notes that, after working with instrument vendors and control-system companies over the past five years, most of Pfizer's vendors' instruments now communicate via OPC.

Another challenge has been ensuring that data from PAT flows into the process-control system quickly enough to enable meaningful control of process fluctuations to keep CQAs within specification. "If the measurement takes longer than the residence time of the material—for example, 30–45 seconds of residence time in the blender—then the measurement can not be used for process control," explains Hausner. He says that available NIR instruments are adequate for some applications, but faster analysis may be needed for other applications, such as smaller doses or lower percentages of API, which would necessitate more scans to obtain a measurement. C-SOPS continues to investigate solutions for NIR measurement in its production-scale Continuous Pharma-

Figure 2: A continuous, high-shear granulation and drying system in operation at the GEA test center (ConsiGma, GEA Pharma Systems).

ceutical Advanced Manufacturing Laboratory (CpAML). Analysis costs are part of the equation, notes Hausner. For example, a current CpAML project is comparing the use of one, fast (i.e., expensive) spectrometer with an array of slower but more economical spectrometers. An alternative method is inferential sensing, in which offline laboratory data is used with known correlations to give the control system the data it needs, adds Thompson.

Tracking material flow through the system is a crucial aspect of process control. A SCADA system tracks the location of a "product plug" as it moves through the process and adds this context to the PAT data in the process-control modeling software, explains Ivo Backx, manager of business and project development for the pharmaceutical industry at Siemens Industry Automation Division. "In tablet production, for example, multiple variables control the CQAs and you need to know what these attributes are and the correlation between them at specific points in the process," says Backx. "For example, you need to know that the material in the tablet press now had a certain content uniformity at the blender." Material tracking through the system is linked to requirements for traceability, notes Backx.

Traceability is simple in a batch system because it is assumed that all the product from one batch is the same. "For a continuous operation, traceability becomes much more important because not all the product is submitted to the same process at the same time. Using a first-in/first-out (FIFO) principle is, therefore, very important," says Schoeters, who notes that GEA has adapted the unit operations of mixing, granulation, drying, compression, and coating in such a way that the product is traceable throughout the production line and back-mixing is limited as much as possible. The ConsiGma system, such as the line shown in **Figure 2**, continuously monitors CPPs to keep them in control and maintain product quality. This includes measurements using PAT (e.g., particle size, moisture, uniformity), but primarily involves monitoring of and control-feedback loops on machine parameters. Torque of the granulator screws, for example, is continuously monitored, and a deviation from the set value triggers actions and alarms.

Other challenges

High equipment costs and restrictions on capital spending are currently barriers to implementing PAT and continuous processing technologies. In addition, revised European regulatory guidance requires refiling of NIR instruments after calibration updates (3). "This new guidance on NIR is very restrictive. It does not allow for changes in raw materials, instrument maintenance, and all the routine occurrences that require calibration maintenance," notes Hammond.

Real-time release

Although real-time release (RTR) is a goal for industry and for regulators, only a few companies have achieved it

as a commercial reality. In RTR, product quality assurance is based on online analysis, and the product is released as it is produced rather than a batch being held while waiting for quality-control testing. RTR could be implemented for batch processing, in that a batch could be released if there were no deviations throughout the batch. In continuous processing, product could be released continually given no deviations. Theoretically, online measurement would identify out-of-specification product and allow it to be segregated or even identify a change in CQAs before the product goes out of specification (4).

A new program, Accelerating Innovative Research (AIR), builds on the C-SOPS infrastructure at Rutgers and is focused on working with existing PAT as well as partnering with companies to move RTR testing technology forward. The program will involve working with large pharmaceutical companies to run specific formulations as case studies in an effort to build up a toolbox of knowledge on how spectroscopic data can be used for RTR testing.

Implementing closed-loop control is a step towards RTR. "Intelligent processes that are proactively controlled to ensure the expected outcome are inherently capable of supporting a RTR strategy. Regulators have always stated that tight control of the unit operations leading up to final product is the best way to ensure quality of the product and enable a RTR filing," says Hammond, who notes that Pfizer's Chantix RTR application is now filed in all major markets and most of the rest of world. "The value of RTR has been reduction in laboratory testing. The focus in the future will be on enabling a modern supply chain, with flexible response to a pull from the market, and maintaining lower inventory."

Many in industry and academia say that continuous manufacturing using online PAT with closed-loop process control and real-time release represent the future of solid-dosage manufacturing. These concepts are part of a "seismic shift in culture change within the pharmaceutical industry, which continues to put the spotlight on manufacturing in a way that has been absent in the past," concludes Freeman.

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Ensuring Sterility of PARENTERAL PRODUCTS

Adeline Siew, PhD

Sterility assurance is of paramount importance in parenteral drug manufacturing. Contamination of parenteral drug products can have serious consequences on the patient. To gain further insight into best practices for sterility assurance, *Pharmaceutical Technology* spoke to James Agalloco, president of Agalloco & Associates and member of *PharmTech's* editorial advisory board; Tim Sandle, head of microbiology at Bio Products Laboratory; and Benoît Verjans, scientific advisor at Aseptic Technologies and member of *PharmTech's* editorial advisory board.

Sources of contamination

PharmTech: What are the most common sources of contamination that can arise in sterile manufacturing or aseptic processing?

Agalloco (Agalloco & Associates): We've known for years that the most common source of contamination has been the operator. There's been a steady progression of technology advances to reduce the problem that the presence of the worker presents. It started with curtains, and has progressed to closed restricted access barrier systems (RABS) and isolators. The next advancement in this area will be the use of robotics and automation to further reduce the impact of personnel.

Sandle (Bio Products Laboratory): Parenteral drug products are required to be free from three things—viable microorganisms, pyrogenic substances, and visible particulates. The different sources of microbiological contamination within clean environments can be divided into water, air, surfaces (both within the room and from equipment), and personnel.

The main risk from water sources is to product formulation and the activities up to and including final sterilization. In my experience, the greatest concern comes from wet equipment, allowing water-borne bacteria such as *Pseudomonads* to grow. Water is a double concern because it is a vector for contamination and a growth source for microorganisms. We cannot avoid water in cleanrooms. Water is a common feature in pharmaceutical processing (e.g., as an ingredient, a cleaning agent, a diluent for disinfectants, and steam supply). Other sources that affect aseptic processing include improperly designed clean air devices and air-flows that can direct microbial-carrying particulate contamination towards the exposed product.

Verjans (Aseptic Technologies): There are two distinct categories of contamination of injectable drugs. Some contaminations are a result of bad practices; in this case, multiple containers are usually affected. These contaminations are identified through outbreak episodes that affect several patients.

The other group of contamination is more insidious because it affects one vial from time to time. The source of contamination is a living organism that managed to penetrate the container at a certain moment and, if not detected, may trigger disease episodes such as septic shock. Because it is a single event, this type of contamination is often classified in the group of nosocomial diseases.

Mitigating contamination

PharmTech: What are the limitations or challenges to current sterilization methods?

Agalloco (Agalloco & Associates): The obstacle we face is the expectation for higher F0 values, increased doses, and tighter filters. There is a belief that if we just make the process a little more lethal or more robust, it will be better. That ignores the whole other side of the process—what it does to the materials we are processing. There is degradation, increased particles, extractables, less mechanical strength, and other impacts that oversterilization can cause. There needs to be more consideration of the negative consequences of what sterilization does. We only need to kill or remove the bioburden once. Overprocessing is rampant and aside from making things look better on the surface, it's actually not something we should be doing. The half-cycle approach to sterilization should be used rarely, and unfortunately its use is becoming more prevalent rather than less.

Sandle (Bio Products Laboratory): The main limitation with any sterilization method relates to the validation, the way it has been executed, and the way the validated sterilization technology is used in practice. One only has to look at the major pharmaceutical contamination scandals of the past 40 years to see this limitation, from the Devonport incident in the early 1970s to the issues surrounding the New England Compounding Center last year, where three lots of methylprednisolone acetate, intended to be injected into the spinal cord as a treatment for arthritis, were contaminated with *Exserohilum rostratum* (2). This incident led to more than 700 reported infections and some 48 deaths, based on figures from the US Centers for

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Disease Control and Prevention. In both these cases, the sterilization equipment was involved. Besides validation issues, various factors (e.g., economic, space, time-to-release) drive the use of different sterilization technologies. The factor, however, is the product and whether it is compatible with the technology.

The lower-risk technologies are terminal sterilization methods. Terminal sterilization is most commonly carried out using steam (moist heat). Risks are often low provided the cycles have been validated thermometrically and biological indicators have been used to show that sterility-assurance levels are at 10^{-6} as a minimum. A number of quality attributes must, however, be carefully checked for each run. Most important is air removal. It is crucial to ensure that all of the trapped air is removed from the autoclave before activation as hot air is a very poor medium for achieving sterility.

The biggest challenge is aseptic filling. There are complications around product filtration relating to the validation of the product through the filter (where the filter needs to be challenged with 10 million cells of a diminutive bacterium); product bioburden; and issues relating to filter failure (for which post-use integrity checks are crucial). There are also the complications of bringing together a sterile product and sterile components (vials, stopper, crimpers) and attempting to fill thousands of vials under a clean air zone.

Verjans (Aseptic Technologies): There is a difference between terminally sterilized and aseptically filled products. For the first category, products are sterilized shortly after fill–finish, thereby eliminating contamination that could potentially put patients at risk. On the contrary, for aseptically filled products, there is a real concern of contamination because the last safety barrier provided by terminal sterilization is not there.

From now, I will exclusively talk about aseptic processing, in particular fill–finish. The following is a list of contamination sources, among others:

- The product may have been contaminated during formulation so all precautions during fill–finish are useless as the contaminant is already there.
- Contamination may occur during product transfer.
- Product contact parts, such as paths or stoppers, may be contaminated.
- The environment may be contaminated during introduction of various elements (e.g., tools).
- The quality of the environment may be at risk due to a tiny leak in high-efficiency particulate air (HEPA) filters or in barrier integrity.
- The operator can bring a contaminant, especially if he is in close contact with the processing area.

To have safe aseptic processing, it is mandatory to address all these aspects carefully, which therefore makes aseptic processing perhaps the most complex pharmaceutical manufacturing process. The challenges are to:

- *Prevent the contamination from coming in contact with the environment:* The best approach is to optimize equipment design, set up clear and sound procedures, and train operators. Training is crucial as, even with the highest quality of equipment and procedures, the process is at risk without good operators.
- *Detect the contamination:* Can we identify the contamination and eliminate it before it reaches and affects the patient?
- *Reduce the probability of transforming a contaminant into a contamination:* The lower the exposure, the lower the risk.

Recent advances

PharmTech: What are the recent advances in equipment design, operation, filtration, or processes that are addressing some of these problems?

Agalloco (Agalloco & Associates): The operational improvements made by increased use of closed RABS and isolators are well known. Increased use of robotics and automation are making aseptic processing safer. Other technologies such as closed-vial filling, gloveless isolators and single-use systems will further enhance performance of aseptic manufacturing. Understanding the importance of bioburden destruction as opposed to biological indicator destruction would help as well.

Sandle (Bio Products Laboratory): Cleanroom technology did not advance greatly until the late 1990s. This pace of transformation has accelerated more quickly in recent years, notably with barrier technology. Aseptic filling risks have been lowered through the use of isolators and RABS. RABS create a physical and aerodynamic barrier to protect the product, but they are not all enclosing. Isolators are the most effective as they create a complete barrier (isolation) between the products and people. Where isolators can be placed around filling machines, it allows for the entire space to be decontaminated using hydrogen peroxide (either as a vapor or in the ionized state). Isolators are not risk free, however, due to issues such as air leakage.

There has been some conceptual changes with cleanroom design, using computer-aided engineering software that can help pinpoint contamination risks. There are also advancements in the use of risk management, supported by initiatives from regulators such as FDA. Risk assessment tools such as HACCP (hazard analysis and critical control points) have become more common. Also with cleanrooms, various items of equipment and surfaces are now manufactured with antimicrobial coatings.

With processing, the most important recent advances have come from single-use disposable technologies. Such technologies have reduced risks by allowing pharma organizations to move away from equipment that need to be sterilized or consumables that are recycled or pose a risk with their transfer into cleanrooms. Single-use items are typically sterilized using gamma rays, which kill microorganisms by destroying cellular nucleic acid.

Verjans (Aseptic Technologies): In the last decade, multiple improvements have been introduced to mitigate the risk of contamination. The first one is to improve gowning of operators moving from classical laboratory coats to fully gowned operators. The second one is to use filters with extremely good efficacy in retaining living organisms, even the smallest ones and the mobile ones. The third one is to separate the operators from the processing area. Processing equipment can now be protected by advanced barriers such as the RABS and the most advanced

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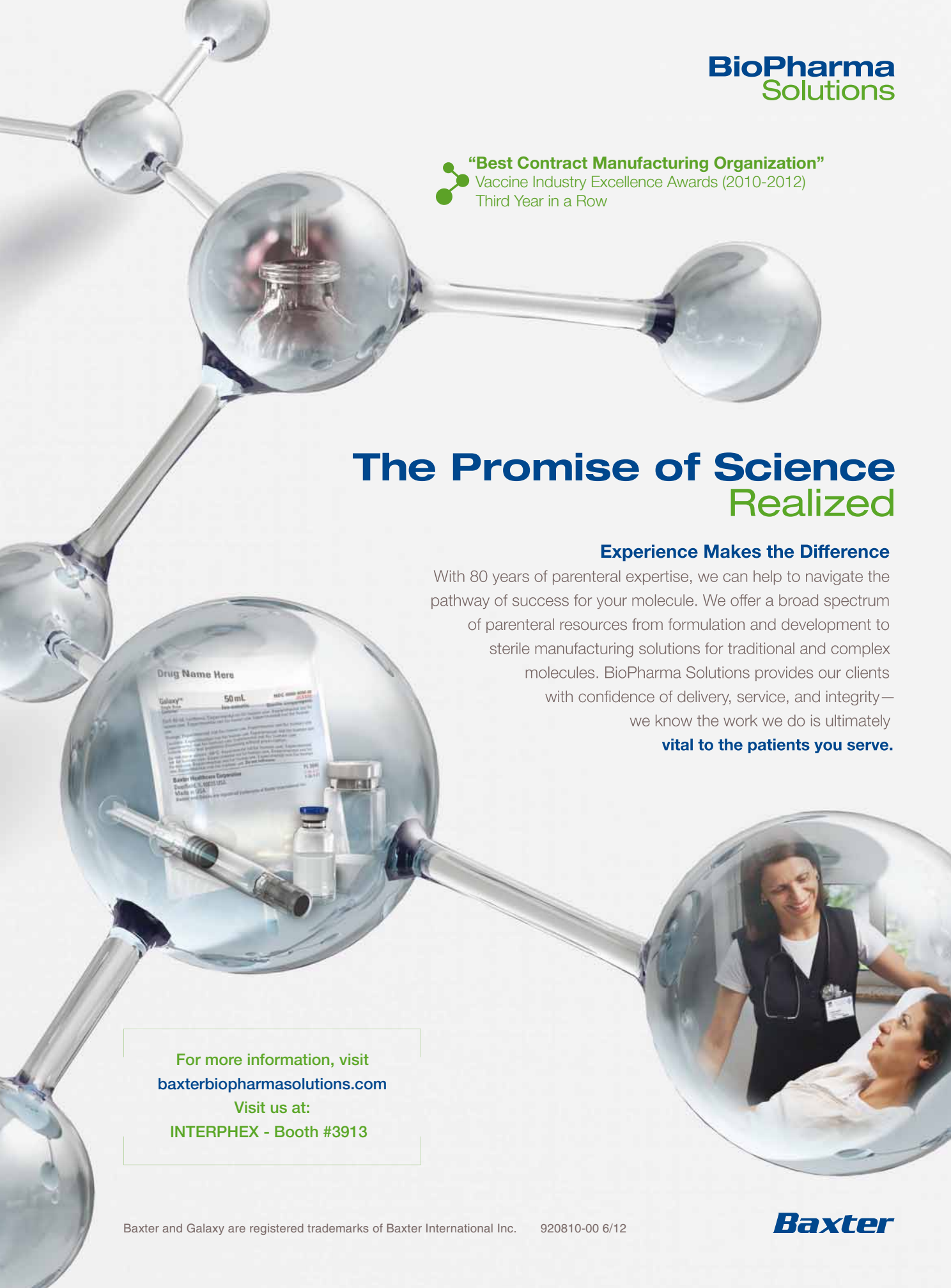

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ones like the closed RABS and isolators. The isolators offer complete separation of the processing area from the environment, combined with an automated sanitization system.

A new category of improvements consists of the reduction of exposure to the environment. Reducing the time when a container is open reduces the probability of having a living organism penetrating into the container. The same concept applies to contact of the inside part of the container. Two new technologies that aim to reduce this exposure include:

• *Blow-fill-seal technology,* based on the concept of forming the container from heated polymer, filling it immediately after cooling and closing it without involving contact with another product part. The process takes a few seconds, thereby minimizing the probability of entry of living organisms.

• *Closed-vial technology,* based on the concept of using a closed sterile container. The stopper, instead of being exposed to the environment, is already in place. Filling is done with a needle piercing the stopper and dispensing the liquid. Immediately after these operations, the container closure integrity is restored by laser resealing of the stopper. It has been demonstrated that this technology reduces the risk due to exposure by more than 100 times compared to open vials (3).

Microbial control

PharmTech: What are the limitations/challenges to current testing methods for microbial control?

Agalloco (Agalloco & Associates): We've exhausted the ability of microbial sampling and test methods to help us. The expected quantities of microorganisms are at or below the threshold of detection for most sampling methods. The only acceptable result in Class 100 (Grade A) is less than 1 colony-forming unit (CFU). There are problems with this because it suggests that aseptic processing has to be conducted under essentially sterile conditions, which is not possible, especially with the manned filling technologies in use. Aseptic processing can be successfully performed in less than sterile conditions, and that creates severe tensions between what we can provide in the way of environmental and process control, and the extreme regulatory expectation of those same controls. Rapid microbial methods aren't the answer, because they only provide the results somewhat sooner.

Sandle (Bio Products Laboratory): Monitoring methods are divided into viable monitoring and nonviable particle monitoring. The objective of viable environmental monitoring is to enumerate the numbers of microorganisms present at a location within a cleanroom, to allow incidents to be recorded and, ideally, to permit species level identification. This type of monitoring is undertaken using a range of different air and surface counting methods, namely active air-sampling using volumetric air-samplers; so-called passive air monitoring

using settle plates; the surface methods—contact plates and swabs; and the monitoring of personnel in terms of gloved hand prints and suit gown plates, taken on exit from the cleanroom suite.

Concerns with these classic methods was highlighted in the recent update to the *United States Pharmacopeia* chapter <1116>, which argued that we need to get away from seeing these methods as somehow 'super accurate' such as an analytical instrument in a chemistry laboratory (2). The methods are limited because they can only be used periodically and thus serve as spot checks only. They cannot pick up all the culturable microorganisms present for example, due to weaknesses in collecting all the microorganisms that adhered to surface when using a contact plate. Recovery is also affected by temperature and agar variations.

As another example, with active air-samplers, these devices are only designed to pick up 50% of the viable particles that are drawn in. There are risks with the method of drawing the air in, such as by impaction or through centrifugal forces, damaging or stressing the microorganism to the extent that it will not grow. It has been estimated that many of the micororganisms present in cleanrooms will not grow using the conventional methods. These are termed the viable but nonculturable (VBNCs) organisms.

These same issues also affect in-process bioburden monitoring, used to measure contamination build-up in process areas, even with end-product sterility tests. There are, however, things that can be done to improve detection. With settle plates, it is important that the plates are tested to show that after exposure, due to the inevitable weight loss from drying out, they can still grow microorganisms. With contact plates used on surfaces, these plates should contain neutralizers to ensure that any residues from cleaning agents do not mask any microorganisms present. With swabs, the method will always be limited. However, there are new types on the marketplace that give better recoveries. Finally, with active air-samplers, tests should be conducted to show that the sampler does not disrupt the air-flow, especially at ISO Class 5.

Verjans (Aseptic Technologies): Let's compare between large particle detection in containers and environmental monitoring. Particle detection is a systematic monitoring that screens all containers. The efficacy of the particle-monitoring process, even if not 100% perfect, is good enough to eliminate all or almost all containers containing a large particle, which is a potential source of embolism for the patient. This approach is not yet feasible with small living organisms and one way to address the contamination risk issue is to have environmental monitoring. This control is essential but presents the disadvantage of being based on samples. For example, contact plates and active air sampling are only targeting one sample of air; hence, the probability of detecting bacteria in the processing environment remains low.

It has been estimated that approximately 28 dm^3 of air are in contact with each 2R glass vial (3). Therefore, classical microbial air monitoring systems collecting 1 m^3 of air are only representative of 35 vials. Knowing that a batch may represent few hundreds of thousands of vials, statistical calculation demonstrates that the probability of detecting a CFU during microbial environmental monitoring is much lower than having one or few contaminated vials.

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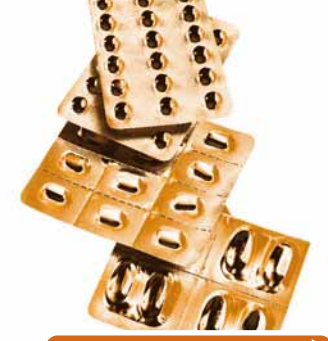
WEB For an expanded version of this article that discusses process analytical technology in microbial control, please visit PharmTech.com, or click on the QR code at the right using your smart phone to go directly to the article.



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Previewing Packaging Innovations

Hallie Forcinio

The annual INTERPHEX show presents end-to-end packaging solutions.

Whatever the packaging requirement, chances are there's a solution waiting at INTERPHEX, the annual pharmaceutical industry trade show scheduled for April 23-25, 2013, at the Javits Center in New York. This year's show is noteworthy for productivity enhancements, anticounterfeiting technology, and quality control options.

Improved productivity

On a single-rotary tablet press from Fette, the design of the compression stations, drive, turret, and tablet discharge cuts changeover time and improves productivity. For example, turret removal requires no tools and takes only 15 minutes. In addition, upper and lower compression rollers and pressure and position settings adjust automatically by means of commands from the operator interface; operators do not need to make manual adjustments after a turret change. The turret also features a coded tablet scraper and coded filling-cam detection as well as a central, multifunction connector for oil, air, and electricity. Equipped with up to 51 stations, the system produces up to 367,000 tablets per hour. The rotor design also supports quick changeover, maximizes yields, and minimizes product loss. The machine is clad in easily detached, FDA-certified, high-performance polymer panels and offers 360-degree access. Geometrically optimized surfaces and an integral vacuum system expedite cleaning. User-friendly operator interface provides swift access to the machine's most important functions via 12 pictogram buttons (FE35 Tablet Press, Fette Compacting America).

Figure 1: Groninger's aseptic vial-filling line offers contact-free container handling.

Figure 2: An AlpVision app enables product authentication via smartphone.

A high-performance liquid-filling machine from Cozzoli Machine combines a small footprint with peristaltic pump and single-use technologies. Single-use elements eliminate cleaning, cut costs, hasten setup, and reduce waste. Designed for Class 100 cleanrooms, the fillers rely on existing overhead laminar air flow and may be specified with two, four, six, or eight heads (VR2PP Series liquid fillers, Cozzoli Machine).

A single-use filling system from Filamatic equips a benchtop filler, compatible with a piston, peristaltic, gear, or lobe pump, with a peristaltic pump. In this configuration, fluid flows in a flexible tube fitted inside a circular pump casing. Since the pumped fluid contacts only the inside surface of the disposable tubing, cleanup is quick and easy. The peristaltic pump works best with moderate to large (50 mL to >1100 mL) fill volumes and achieves +/- 1% accuracy (AdaptaFil semiautomatic benchtop filler, Filamatic).

Romaco's family of liquid filling machines includes six models that handle vials and bottles ranging from 2–500 mL at speeds of up to 200 containers per minute. Features include multiple dosing system and volumetric pump options, adjustable positive container transport for fast changeover, multiple closure stations and cap feeding systems, and programmable setup and recall of product recipes and production parameters. The systems integrate seamlessly with labelers and cartoners (Romaco Macofar LF-200 Series liquid filling machines, MG America, subsidiary of MG2).

We'll be seeing more ...

- Anticounterfeiting tools
- Product authentication via smartphone
- Turnkey filling lines
- Filling systems compatible with more than one pump system
- Single-use product paths

FIGURE 1 COURTESY OF GRONINGER USA. FIGURE 2 COURTESY OF ALPVISION

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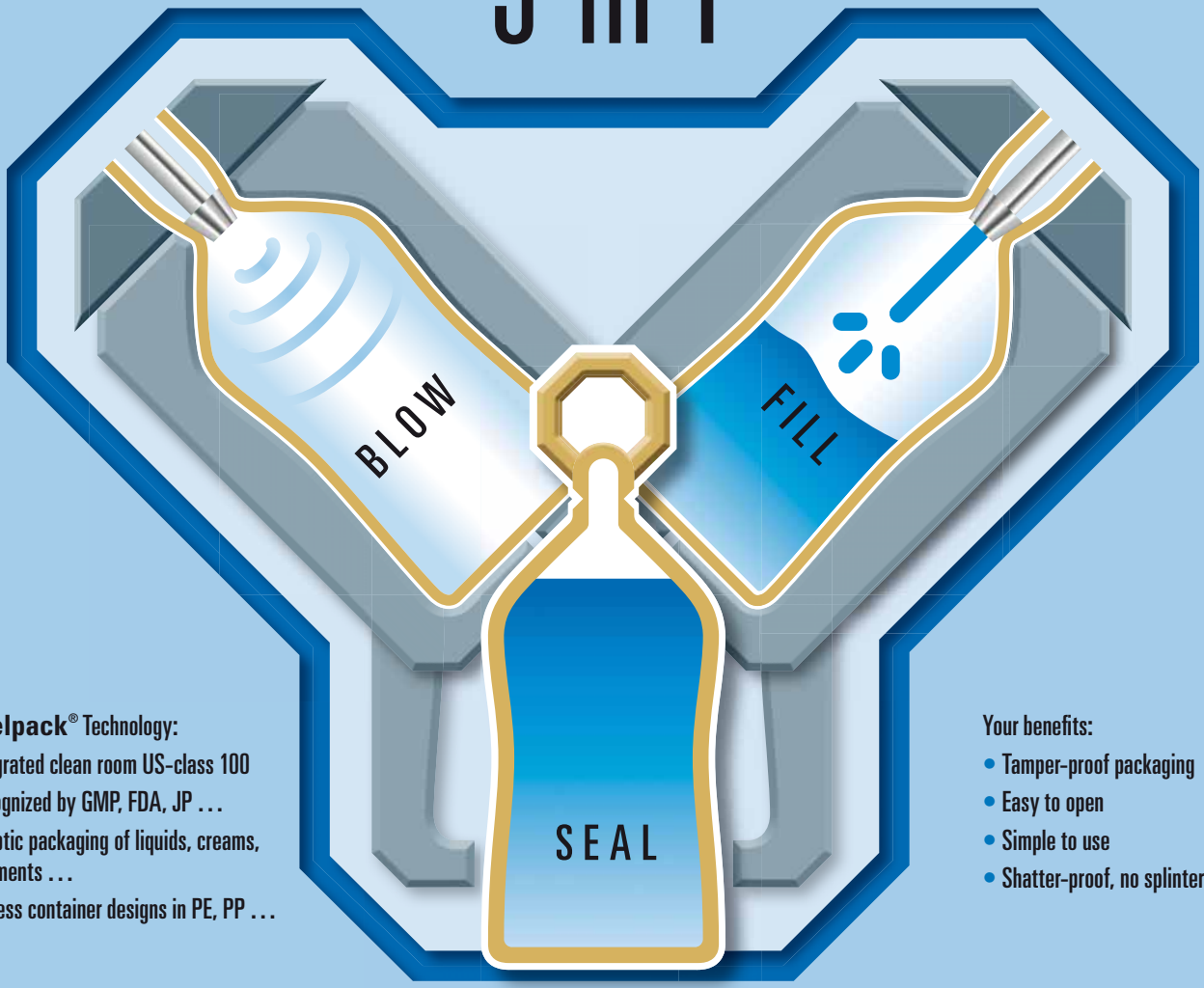

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Figure 3: Schreiner MediPharm's Pharma-Comb Security Label helps prevent counterfeiting.

Figure 4: A carton from RondoPak has a tamper-evident design.

Figure 5: Pharma Technology's AIO All In One Deduster and Tester System measures tablet characteristics.

Groninger's high-speed, aseptic vial-filling line handles 400 vials per minute. Compatibility with time-pressure, rotary piston, and peristaltic pumps increases system flexibility and allows it to fill different products. A vial-handling system eliminates damage and noise associated with glass-to-glass contact (see **Figure 1**). A three-fold camera checks for glass particles, residues, or deposits inside the vial to prevent contamination of the product and also can inspect filling and closing steps (Kombi Filling Rack on vial filling line, Groninger USA).

A high-speed line from Marchesini Group, capable of filling parenteral products at 400 vials per minute, consists of a rotary washing machine, depyrogenation tunnel, and filling/stoppering machine. The eight-station rotary washer cleans ampules, vials, and other round containers and features quick size-changeover. A modular design accommodates the addition of an ultrasonic prewasher, silicone applicator, heat exchangers, filters, automatic valves, automatic drainers, pressure transmitters, and unloaders to tunnel or tray. The continuous-motion depyrogenation tunnel relies on modular design as well as hot-air flow. A pressurization system independently controls conditions in different sections of the tunnel. Proprietary cooling-zone sterilization cuts cycle time in half. The continuous-motion, in-line filler/capper features an ultra-clean balcony design and is compatible with restricted access barrier systems and isolators, as well as clean- and sterilize-in-place configurations. Other features include contact-free vial handling, camera inspection, and checkweighing. Pump options include peristaltic, time-pressure, and volumetric (WR24 washing machine, Depyr601 tunnel and Stery LC filling/stoppering machine, Marchesini Group).

Anticounterfeiting and tamper evidence

Smartphones help fight counterfeiting with an app designed to authenticate products in three seconds. As shown in **Figure 2,** the phone is positioned over packaging or molded parts to detect and verify covert safety features (e.g., taggants or microprinting, which looks like part of the graphics but reveals a message when examined under magnification). The verification action also can deliver information to the user/consumer about product features, user data, and market (smartphone authentication app for Cryptoglyph and Fingerprint covert safety features, AlpVision).

Schreiner MediPharm's peel-off label for vials now includes a security version with overt and/or covert features to authenticate product and help prevent counterfeiting (see **Figure 3**). The mix of security elements can be customized and often can be added without changing the label design. Options include overt elements, such as holograms, color-shifting security inks, and guilloche patterns, as well as covert tools, such as voiding effects and LaserSecure, which relies on pigments that only can be "seen" by a dedicated handheld reader. The label also incorporates detachable segments for patient record updating and other purposes. For extra security, removal of detachable sections from the substrate reveals the message, "peel-off part has been removed" (Pharma-Comb Security Label, Schreiner MediPharm).

Another anticounterfeiting tool, a proprietary, two-dimensional barcode from Complete Inspection Systems, matches and verifies GS1 codes printed during packaging operations. The data-intensive barcode can provide information about the location of covert codes used for product authentication (HD P.A.S.S. Barcode Solution, Complete Inspection Systems).

Rondo-Pak's tamper-evident carton design opens and recloses as easily as a standard folding carton and can be erected and loaded at the same speed as a conventional folding carton (see **Figure 4**). Perforations cause the lid and dust flaps to tear. The design reportedly surpasses first-opening verification security requirements of the Falsified Medicines Directive 2011/62/EU, which take effect in 2016 (tamper-evident folding carton, Rondo-Pak).

Quality control technology

A quiet (less than 70 decibels), compact tablet-deduster and testing system from Pharma Technology combines multiple functions such as segmented deduster spirals and metal detector on one base (see **Figure 5**). The high precision, in-process tablet tester checks weight, hardness, and thickness by sampling at regular intervals and feeds test data to the tablet press for recording into the batch record. Testers can be positioned on three sides of the base and offer push-fit, cable-free connections for power and data storage. A washable, exchangeable deduster module minimizes changeover time (AIO All In One Deduster and Tester System, Pharma Technology). **PT**

FIGURE 3 COURTESY OF SCHREINER MEDIPHARM. FIGURE 4 COURTESY OF KÖRBER MEDIPAK. FIGURE 5 COURTESY OF PHARMA TECHNOLOGY.

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Bio/Pharmaceutical Facility Design and Operation: A Primer

A Q&A with Michael Lacey of the National Institute for Bioprocessing Research and Training

This article is excerpted from an article in a series of primers with training experts from the National Institute for Bioprocessing Research and Training (NIBRT) published in *BioPharm International* (1). NIBRT provides training, educational, and research solutions for the international bioprocessing industry in facilities located in South Dublin, Ireland. The Institute is based on a collaboration between University College Dublin, Trinity College Dublin, Dublin City University, and the Institute of Technology Sligo. Michael Lacey is plant manager at NIBRT and is responsible for facility, equipment maintenance, and support services to the plant's core business of bioprocessing, training, and research. Although this interview focused on biopharmaceutical facilities, the advice is applicable to any pharmaceutical facility.

Facility planning

PharmTech: What do bio/pharmaceutical companies just starting out need to keep in mind in terms of planning a new facility's location and construction?

Lacey: There are many factors to consider in terms of choosing location, but some are crucial. First, the reality is that finance and commercial aspects are major considerations. The second category I would look at is the infrastructural side and the existence of support services. Finally, for me perhaps, the most important factor to consider is the people who run the factory. People are the most important asset a company has.

Michael Lacey is plant manager at NIBRT, Fosters Avenue, Mount Merrion, Blackrock, Co. Dublin, Ireland.

To expand on those three categories, let's look briefly at the financial and commercial side of things. Corporations are interested in corporate taxes, local taxes, and charges that they will pay in a particular location. They will be looking at their transfer pricing policy. They may have a treasury strategy. They may set up their financial headquarters in a particular location alongside their manufacturing base.

Companies will surely look at the availability of granted training support, and they will be very interested in their cost base; that is, the cost of labor, salaries, wages, transport, and shipping. Very importantly in the European context, companies will be interested in access to markets in certain countries, particularly European Union countries.

Looking at the infrastructural and support services side of things, manufactured product must be brought to the market. Therefore, effective distribution, including storage and freight transport by road, rail, air, and sea, are very important. With regard to a specific location, a company may prefer to set up where there is already a cluster of similar clients with similar requirements. If such a cluster exists, there is likely to be support services available, such as laboratory services, maintenance services, project management, and regulatory expertise as well as educational and research support from nearby institutes and colleges.

The third category, people, is based on who will operate and manage the plant. It is crucial to have a strong pool of talented people who are well-educated, experienced, and flexible. Those people should also have continuing access to training and education.

Energy management

PharmTech: In terms of specific facility operations, can you address the common needs for energy management in bio/pharmaceutical manufacturing? Also, what key things should companies look for when planning for these systems?

Lacey: Energy management is becoming increasingly important across the industry given the strong green agenda worldwide and the need to reduce carbon footprint. There is also a very strong need to reduce cost base, and energy cost is a major portion of the operational cost of most pharmaceutical plants. Companies fall into a number of categories in terms of how they manage energy. For example, there are companies who manage energy very well according to national and international standards. They dedicate resources to energy management, and these resources make a big difference to operating cost. There are other companies who engage in energy projects and do quite well in terms of saving money, but perhaps, don't manage energy in a structured way. And then there are those companies who do not address energy issues at all.

Overall, energy must be factored into plant design and construction. It's particularly relevant to those who are looking at inward investment in new plant construction. New plant construction provides an opportunity to get energy management right. The problem that the industry faces

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in designing a plant is that it must comply with cGMPs and must be validated. Requirements for energy-usage reduction can sometimes conflict with cGMPs, for example, in relation to air changes, but I am convinced based on my experience that designers, production teams, quality teams, and engineering teams can work together to deliver an energy-efficient plant that is also GMP compliant.

PharmTech: What other factors are at play with energy systems and cost?

Lacey: There are many opportunities to make gains in terms of the building, such as good insulation and draft-proofing, use of solar gains, natural lighting, intelligent lighting, compressed air usage, an optimum strategy for HVAC (heating, ventilation, and air conditioning), and use of alternative energy sources. HVAC systems are major energy users due to the requirement to make air changes in rooms and to condition the air. Air changes represent scope for cost savings. For example, if you have a Grade B room with a national requirement of 20–30 air changes per hour, the air change rate should be critically reviewed to suit the operation. At the building-design stage, room sizing (i.e., volume) should also be optimized. Thus, the air moved and conditioned can be minimized and so minimize energy usage. Most HVAC systems in pharmaceutical processing applications are "once-through". However, the use of recirculation systems should be adopted where possible as these are less expensive to run. Finally, room temperature control is key to optimizing energy usage. Room temperatures should be selected to suit the process and/or occupants.

Lighting is an appreciable proportion of a plant's energy usage. High-frequency fluorescent systems allow for dimmable lighting, so facilities can use dimmers to control the lighting in a way that it reacts to ambient light level. If a building has natural light, the fluorescent lighting levels can be dimmed accordingly. Lighting in public areas should react to presence and ambient natural light. "Intelligent lighting systems" should be considered.

Air compressors represent another area of opportunity for cost savings. Companies should analyze their air usage, and maybe use two or more smaller compressors rather than a single larger one. They should have variable-speed drives (VSDs) to allow maximum flexibility of response to demand. Most importantly, plant managers should ensure air leaks are repaired, as leaks can represent up to 30% of compressed air generation, and contribute significantly to energy wastage. In a medium size plant of 10,000 m^2, it can cost something like EUR 60,000–70,000 (approximately $78,000–$91,000) per year to run a compressor.

Lastly, it's important to train staff about energy management. People use energy, and if they are taught good habits (e.g., turning off lights and monitors), then money can be saved.

HVAC systems are major energy users due to the requirement to make air changes in rooms and to condition the air.

PharmTech: You mentioned using two smaller air compressors instead of one larger unit. What benefit does this provide?

Lacey: As I mentioned, an air demand analysis needs to be done before that decision is made. Your air compressor supplier can do this for you. This improves response and "scalability" between air demand and compressor running. One plant I worked with had a single large compressor supplying the entire factory and had a fixed-speed drive. The problem with this is that the motor either runs 100% or is off completely. This means that a large motor has to stop and start in response to changes in demand, and this is not energy-efficient. A smaller unit fitted with a variable-speed drive can respond more flexibly. Using two smaller compressors also means that you have a backup in case one unit fails.

Water systems

PharmTech: What considerations does a company need to make with setting up and maintaining bio/pharmaceutical-plant water systems?

Lacey: Pharmaceutical water technology is well-established with a large number of reputable and capable designers and providers available. For purified water (PUW), a good system will invariably include reverse osmosis (RO) and electrodeionization (EDI), with ozone as a sanitizer. It is critical that the raw water is carefully considered and factored into design; not enough attention is given to the quality of mains water and the pretreatment of it. I can highly recommend ultra-filtration (UF) as a pre-treatment technology; we have installed this in NIBRT with excellent results. For water for injection (WFI), distillation is mandatory in Europe and almost the norm everywhere. It's important to get the system sizing correct, especially if considering multiple-effect stills. For maintenance, it is important to get specialist help from the vendors; however, I can't over-emphasize the importance of comprehensive in-house monitoring by doing daily and weekly checks. This is a basic form of condition-based monitoring and is very effective.

Environmental aspects of water systems can be somewhat overlooked. We have talked about energy wastage; however, we also use and waste quite a bit of water in this industry. Pharmaceutical plants are generally metered by local authorities, and they are charged by the cubic meter for water. This can be wasted in fairly innocuous ways. For example, PUW or WFI distribution loop pumps usually have "flushed" mechanical seals and the flushed water goes down to drain. It will look like a small flow, but this can drain a large tank over an extended period over 24 hours. The same applies to ozone sensors that are also flushed. So we waste a lot of PUW and WFI, which costs money, and depending on the location and the type of water plant, the cost can be very high—PUW is estimated to

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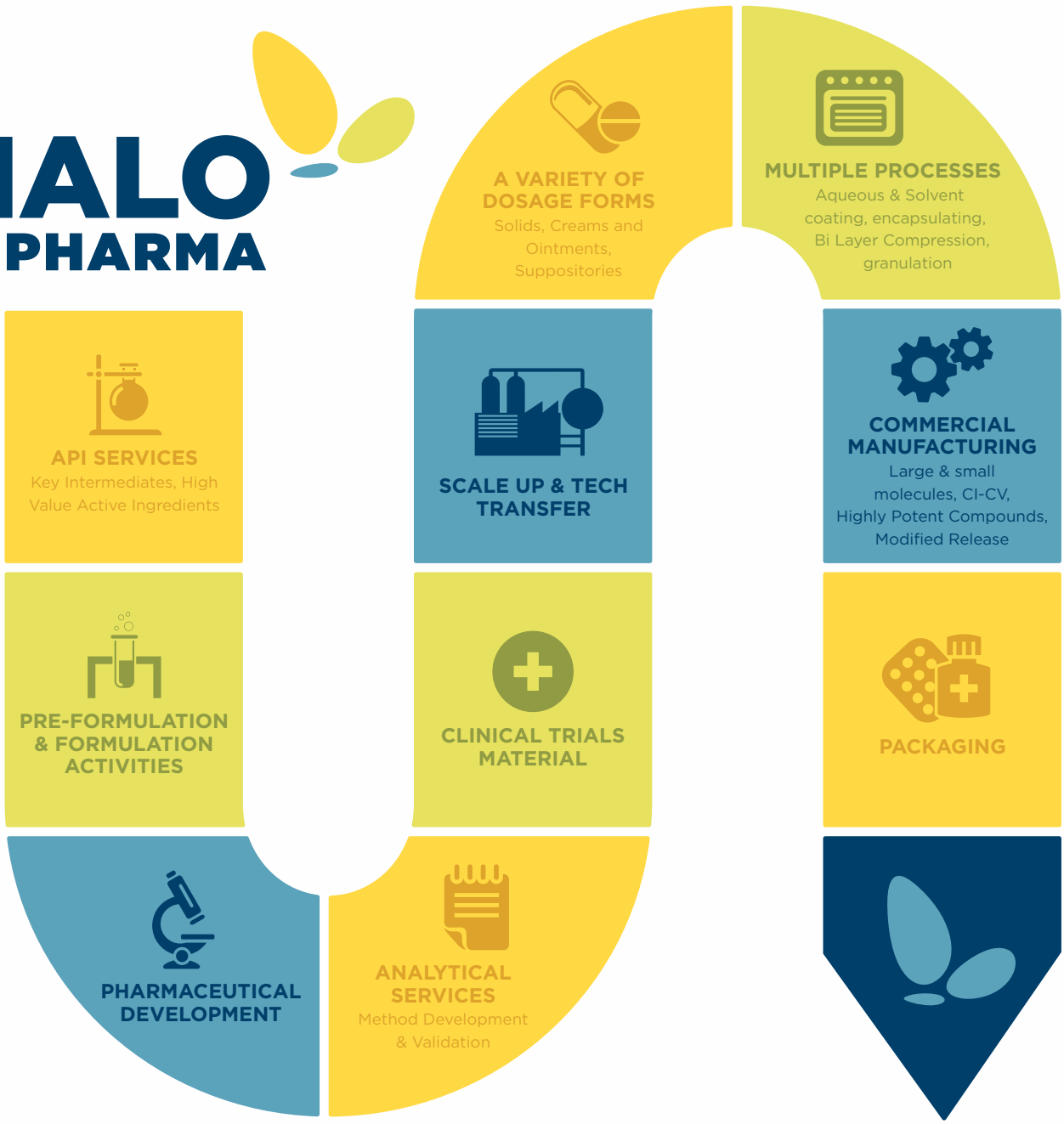

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cost more than 60 cents per L and WFI is more expensive, and so consider the cost of the loss of a 10,000-L tank.

In terms of process, clean-in-place (CIP) is a common technology used in biopharmaceutical plants. It has the significant side benefit that it uses water efficiently. This technology is repeatable and reliable.

Of course we use water for more mundane reasons also (e.g., drinking, washing, toilets). There are automated water controls that can be well utilized to save on water and cost.

GMP Certification

PharmTech: GMP certification is important for the industry. What key GMP and cleanroom considerations need to be kept in mind if a company is trying to obtain GMP certification for its facility?

Lacey: The key points in terms of GMP are that the facility must suit the operations being carried out and must minimize any possibility of errors and contamination. Achieving this is all about adopting best-practice conceptual and detailed design, and so the design process is crucial. Assuming the right teams are in place with the appropriate skills and experience, the current building and process technology is such that, while it is an onerous task, it is relatively straightforward technically to build and validate a facility. Given the nature of our business, a somewhat conservative approach is best.

The increase in single-use and containment technologies offers opportunities. Where before critical operations may have taken place in a Grade A environment with Grade B background, newer technologies means that we can use rooms with a lower classification which are more cost-effective to build, maintain, and operate due to reduced energy usage, filtration requirements, and so on.

Communication

PharmTech: Communication is crucial. Could you comment on this based on your experience?

Lacey: Good and effective communication is probably one of the single greatest needs in a company and not every company does it too well. Companies have to maximize teamwork within their operations, and good communications are vital. Communication needs to be two-directional (i.e., top-down from management with an opportunity for staff to respond and put forward ideas). I strongly encourage meetings and briefings at the operations level, daily, and weekly. Verbal communication is so important, person-to-person and face-to-face. Email is a very useful tool; however, all too often it is a poor substitute for verbal interpersonal communication; that is a skill we should maintain and develop. People are our principal assets and companies need to put a strong effort into developing people and developing communications and teamwork.

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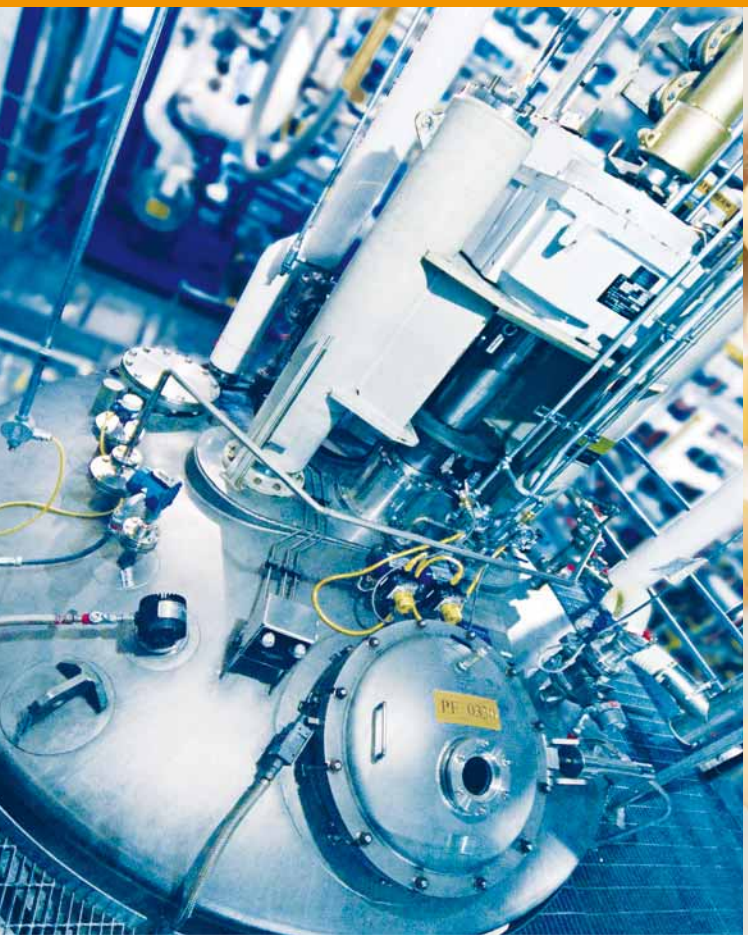

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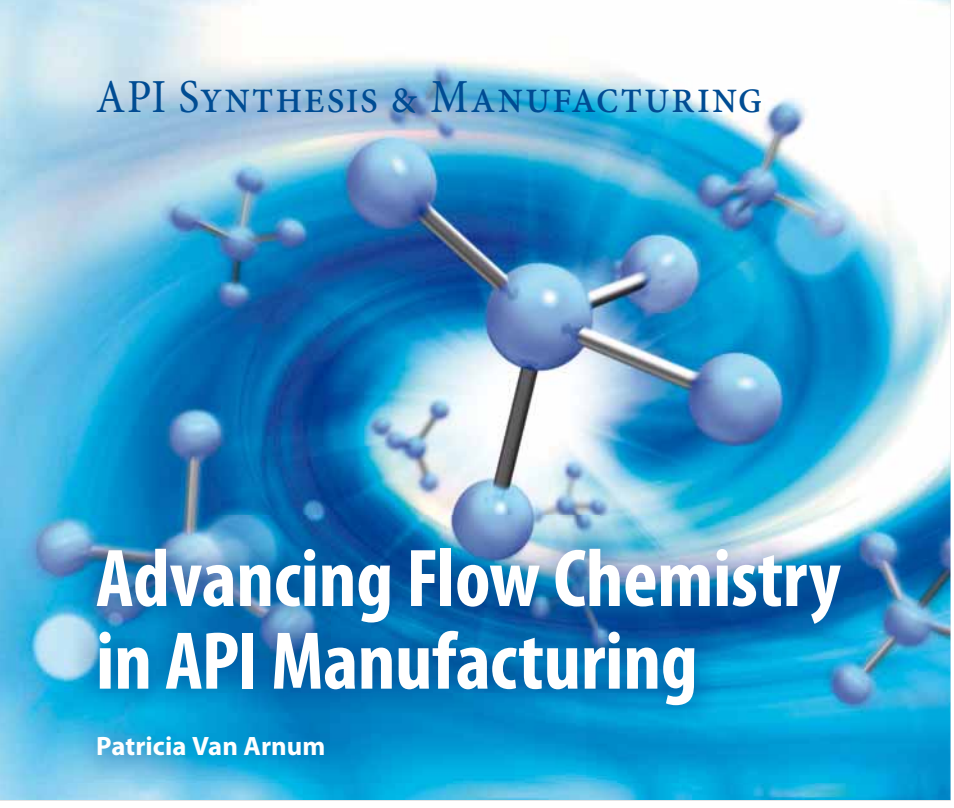

Advancing Flow Chemistry in API Manufacturing

Patricia Van Arnum

Continuous flow chemistry offers potential for greater control, improved safety and environmental profiles, and efficient chemical transformations.

Continuous-flow technology involves the continuous introduction of a stream of chemical reactants into a flow or microreactor to yield a desired reaction product on a continuous basis (1, 2). Continuous-flow technology offers potential advantages compared with traditional batch manufacturing of pharmaceuticals, such as greater optimization and control of the process, improved safety and environmental profiles for a given process, and a reduced manufacturing footprint (1,2). Pharmaceutical companies, fine-chemical producers, and academia are pursuing continuous-flow chemistry in the production of APIs and related relevant reactions with several interesting developments in this field.

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Evaluating the technology

In general, microstructured devices with small internal volumes and high surface-to-volume ratios offer transport capabilities for rapid mixing, enhanced heat transfer for good temperature control, and intensified mass transfer (1, 3). Microstructured devices operate in a continuous-flow environment, which can provide controlled process conditions, high flow rates, and high mass throughput. Continuous operations also may allow for bulk-chemistry processes to have high production capacities. Fluid dynamics determine the characteristics of continuous-flow equipment, such as pressure loss, heat-transfer characteristics, residence time, and mixing time (1-4). The high surface-area-to-volume ratio comparative to a batch reactor enables better temperature control overall, including for exothermic reactions, which improves processing conditions. Scale-up issues may be minimized due to maintaining improved mixing and heat transfer.

Recent activity

These benefits are attracting investment and R&D in continuous-flow chemistry. In February 2013, DSM Pharmaceutical Products signed an agreement with Chemtrix, a supplier of flow-chemistry equipment and services, for providing equipment, development, and manufacturing services to the pharmaceutical industry. Chemtrix specializes in ready-to-use laboratory and kilo-scale microreactors as well as reactor and process design for industrial reactors. DSM provides drug-synthesis route development, scale-up, and implementation of continuous-flow processes for manufacturing. DSM has FDA approval for using microreactors for making a pharmaceutical product at commercial scale under cGMP at its facility in Linz, Austria, where its dedicated commercial-scale installation is located. Initially, the DSM–Chemtrix collaboration will offer an industrial flow process-development package for customized scalable flow-chemistry solutions. The package covers all phases of process design, scanning chemistries, chemistry development, route scouting, equipment design, and scale-up for fully continuous or integrated processes.

Reflecting growing interest in microreactor technology for fine-chemical manufacturing, Lonza invested in what it terms the "Factory of Tomorrow," at its facility in Visp, Switzerland. The investment, made in 2012, enables production of multitons of intermediates and/or APIs based on continuous-flow processing. Lonza operates assets that can produce several kilograms to several tons of small-molecule APIs using microreactors, and the new unit in Visp adds an integrated solution where all common unit operations in flow can be streamlined in a flexible fashion using microreactors (FlowPlate, Lonza) (1). This new unit integrates a range of flow reactors, such as continuous stirrer-tank reactors or ultrasounds and streamlines flow processes, including work-up unit operations, such as liquid–liquid extraction and distillation (wiped-film, thin film). Higher pressure applications are enabled as well by allowing gas–liquid reactions, such as ozone and HCN chemistries. The technology can be used for chemical reactions under severe and extreme conditions, such as high temperatures or cryogenic conditions (1).

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Technology advances

Scientists at Eli Lilly recently reported on reactions in a continuous mode in plug-flow tube reactors (PFRs) to enable chemistry that would be difficult to perform by means of batch processing. Specifically, they developed two different continuous flow approaches for producing a 1*H*-4-substituted imidazole intermediate. In a first-generation approach, rapid optimization and scale-up of a cyclization reaction was shown in a PFR under GMP conditions to produce 29 kg of protected product. This material was further processed in batch equipment to deliver the di-HCl salt. This approach showed the development of chemistry in research-scale PFRs and speed to material delivery through linear scale-up to a pilot-scale PFR under GMP conditions (5). In a second-generation effort, a more efficient synthetic route was developed, and PFRs with automated sampling, dilution, and analytical analysis allowed for reaction optimization of a cyclization reaction and thermal removal of a Boc protecting group. This work culminated in 1-kg demonstration runs in a 0.22 L-PFR for both continuous steps and showed the potential of commercialization from a laboratory hood footprint (1–2 metric tons/year), according to the researchers (5).

In another project, researchers at Eli Lilly reported on a fully continuous process, which involved an asymmetric hydrogenation reaction operating at 70 bar hydrogen, aqueous extraction, and crystallization that was designed, developed and demonstrated at pilot scale. Production of 144 kg of product was made in laboratory fume hoods and a laboratory hydrogenation bunker over two continuous campaigns (6). Maximum continuous flow vessel size in the laboratory hoods was 22-L glassware, and maximum PFR size in the bunker was 73 L (6). The researchers reported that main safety advantages of running the hydrogenation reaction continuous rather than batch were that the flow reactor was smaller for the same throughput, and the tubular hydrogenation reactor ran 95% liquid-filled at steady state. The amount of hydrogen in the reactor at any one time, therefore, was less than that of batch. Additionally, a two-stage mixed suspension–mixed product removal cascade was used for continuous crystallization (6). The researchers reported that impurity rejection by continuous crystallization was better than by batch because scalable residence time and steady-state supersaturation allowed for repeatable control of enantiomer rejection in a kinetic environment (6). The researchers reported that a fully continuous wet-end process running in a laboratory infrastructure achieved the same weekly throughput that would be expected from traditional batch processing in a plant module with 400-L vessels (6).

Researchers at Eli Lilly recently reported on continuous-flow approaches for producing a 1H-4-substituted imidazole.

Researchers at the Massachusetts Institute of Technology (MIT) recently reported on the application of compact crystallization, filtration, and drying for producing APIs. Specifically, they developed a combined crystallization and hybrid filtration-drying-dissolution apparatus for a compact manufacturing platform. Crystallization experiments using a conventional stirred tank and a newly designed scraped surface crystalliser showed advantages in terms of crystallization rates, yields, and the ease of automation (7).

The scraped surface crystallizer used an anchor impeller to create a closed clearance between the crystalliser wall and impeller. The researchers reported that the design prevented crystallization on the wall, generated large crystals to facilitate filtration, and improved draining and washing for automation. The hybrid device intensified three unit operations (filtration, drying, and dissolution/suspension) into a single unit. Intensifying these unit operations potentially reduces the time and material lost due to pumping and reduces contact between the API, the environment and operators. Postcrystallization operations were operated step-wise using the custom hybrid device that delivered satisfactory results for each operation. Fluoxetine HCl was dried in less than 20 minutes, with 99% yield after dissolution in a liquid excipient (7).

Effectively applying continuous-flow technology involves a multidisciplinary approach of chemistry and engineering. As an example, other MIT researchers reported on the development of a Suzuki–Miyaura cross-coupling reaction in a continuous-flow microreactor system. Suzuki coupling is a palladium-catalyzed coupling between organoboron compounds and organohalides and is an important reaction in organic chemistry in general and for pharmaceutical compounds specifically. The researchers developed a continuous-flow Suzuki–Miyaura cross-coupling reaction that started from phenols and produced various biaryls in good yield using a microfluidic-extraction operation and a packed-bed reactor. The project used a multidisciplinary approach with the research on microreactor technology developed by a team led by Klavs F. Jensen, department head, Warren K. Lewis professor of chemical engineering, and professor of materials science and engineering at MIT. The organic synthesis portion of the project was developed by a group led by Stephen Buchwald, Camille Dreyfus professor of chemistry at MIT (1, 4, 8, 9).

Other developments

Scientists at LyraChem, based in Newcastle-upon-Tyne, United Kingdom, and Newcastle University reported on intensified azeotropic distillation as an approach for optimizing direct amidation (10). The direct synthesis of amides from the corresponding car-

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boxylic acids and amines was shown to operate under varying degrees of mixed kinetic and mass-transfer rate control when water was removed by azeotropic distillation (10). A systematic approach was developed to quantify the contribution of boil-up rate to conversion rate and decouple the physical rates from the chemistry. Intensive boiling was used to improve the removal of water during azeotropic distillation and enhance conversion. The researchers reported that some acylations previously thought to be difficult or impossible could be achieved in the absence of coupling agents under green conditions. A cascade of continuous stirred-tank flow reactors operating under intensified conditions was assessed for scale-up of direct amidation reactions and compared to a production-scale batch reactor. The researchers reported that the use of the continuous stirred-tank flow reactors operating under intensified conditions could provide the necessary high rates of heat transfer and, therefore, offer advantages over a conventional batch reactor system (10).

Asymmetric synthesis is an important area of research for producing single enantiomer drugs. Researchers in the Department of Chemistry, School of Science at the University of Tokyo, recently reported on the use of continuous-flow chemistry with chiral heterogeneous catalysts in asymmetric carbon–carbon bond formation (11). They developed and applied a chiral calcium catalyst based on calcium chloride with a chiral ligand to the asymmetric 1,4-addition of 1,3-dicarbonyl compounds to nitroalkenes as a model system (11). The researchers sought to improve the low catalyst turnover number (TON) of asymmetric carbon–carbon bond-forming issues (12). To address product inhibition, the calcium catalyst was applied to continuous flow with a chiral heterogeneous catalyst. The continuous-flow system, using a newly synthesised, polymer-supported Pybox, was successfully used, and the catalyst TON was improved 25-fold compared with those of the previous $Ca(OR)_2$ catalysts (11).

Japanese researchers applied a flash-chemistry approach using flow microreactors to produce a highly reactive palladium catalyst for a Suzuki–Miyaura coupling.

Researchers at the Department of Synthetic and Biological Chemistry in the Graduate School of Engineering, Kyoto University Nishikyo-ku, in Kyoto, Japan applied a flash-chemistry approach using flow microreactors to produce a highly reactive palladium catalyst with a tri-*tert*-butylphosphine (tBu$_3$P) ligand for a Suzuki–Miyaura coupling (12, 13). The flash chemistry enabled the use of highly reactive unstable species as a catalysts for chemical synthesis. Fast micromixing of a solution of [$Pd(OAc)_2$] and that of tBu$_3$P in an 1:1 mole ratio gave a solution of a highly reactive unstable species, which was transferred to a vessel by using a flow microreactor, in which Suzuki–Miyaura coupling was conducted (13). The coupling reactions were completed in 5 minutes at room temperature, thereby preventing deboronation of the used aryl and heteroarylboronic acids (12).

In another study, researchers from the Institute of Science and Technology in Ikoma, Japan, and the School of Pharmacy and Molecular Sciences at James Cook University in Townsville, Australia reported on the diastereoselective [2+2] photocycloaddition of a chiral cyclohexenone with ethylene in a continuous flow microcapillary reactor (14). The researchers reported that the microcapillary reactors have higher conversions and selectivity than the batch system even after shorter irradiation times due to better temperature control, light penetration and generation of gas–liquid slug flow with improved mass transfer in the microreactor (14).

In another development, researchers at the Institute of Organic Chemistry at Aachen University in Germany reported on the asymmetric organocatalytic hydrogenation of benzoxazines, quinolines, quinoxalines and 3H-indoles in continuous-flow microreactors using Fourier transform infrared (FTIR) spectroscopy in-line analysis (15). Reaction monitoring was achieved by using an in-line ReactIR flow cell, which allowed for optimization of the reaction parameters. The researchers reported that the reductions proceeded well, and the desired products were isolated in high yields and with good enantioselectivities (15).

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Method Validation by Design to Support Formulation Development

Mark Alasandro, Thomas Little, and Jeffrey Fleitman

The authors describe a method-validation-by-design (MVbD) approach to validate a method over a range of formulations using both design-of-experiment and quality-by-design principles to define a design space that allows for formulation changes without revalidation. The approach provides the required International Conference on Harmonization validation elements as well as information on interactions, measurement uncertainty, control strategy, and continuous improvement. Despite being less resource intensive than the traditional validation approach, quality is not compromised. Additionally, through judicious planning, the MVbD approach can encompass early formulation design efforts so that a wide range of formulations is taken into consideration when defining the method-validation design space.

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Analytical method validation is a crucial part of formulation development. It is needed to ensure that methods provide accuracy and precision in detecting formulation differences in drug dissolution, stability, active, and impurity levels. Method validation is also key to meeting requirements of cGMP, compendia, and the International Conference on Harmonization (ICH) for testing and releasing clinical or commercial dosage forms. During early development, formulations are often changed to adapt to new preclinical and clinical data. Revalidating each of these new formulations is resource intensive and affects development timelines.

The ICH Q2 (R1) validation guidelines (1) do not provide crucial information such as how formulation changes affect method performance or what method critical validation parameters need to be monitored and controlled. An ICH approach may not provide a good understanding of a method-measurement uncertainty, which is needed to ensure that the overall process capabilities are met and that appropriate in-process controls and specifications are set. This sort of understanding is needed to meet FDA's process validation guidelines (2). Once the product acceptance criteria are established, the influence of assay variation can be determined relative to product acceptance rates.

This article describes a method-validation-by-design (MVbD) approach to validate a method over a range of formulations. It uses both design-of-experiment (DOE) and quality-by-design (QbD) principles to define a design space that allows for formulation changes without revalidation. The approach provides the required ICH validation elements as well as information on interactions, measurement uncertainty, control strategy, and continuous improvement. This approach is less resource intensive than the traditional validation approach without compromising quality. Additionally, through judicious planning, it can encompass early formulation design efforts so that a wide range of formulations can be used to define the method-validation design space.

MVbD enablers

MVbD is not specifically addressed in ICH; however, it is supported by the principles presented in ICH Q8, 9, 10, 11 (3–6) as well as ICH Q2 (R1). There are other industry guidelines (2), publications (7–9) and presentations (10–15) that support a QbD/DOE approach for analytical method development and validation, including FDA's 21st Century Quality Initiative, which was first presented in 2001 and later updated in 2005 (15), and the outcome from FDA's QbD pilot.

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Table I: Hypothetical range of formulations. The API, preservative, and Excipient 3 are varied. Q.S. = Quant satis (quantity sufficient).

Ingredients (% w/w)	Placebo formulation	0.005% API formulation	0.01% API formulation	0.015% API formulation	0.02% API formulation	0.025% API formulation
API	0	0.005	0.01	0.015	0.02	0.025
Preservative	0.01 or 0.03	0.01 or 0.03	0.01 or 0.03	0.01 or 0.03	0.01 or 0.03	0.01 or 0.03
Excipient 1	0.3	0.3	0.3	0.3	0.3	0.3
Excipient 2	0.02	0.02	0.02	0.02	0.02	0.02
Excipient 3	0.5 or 0.8	0.5 or 0.8	0.5 or 0.8	0.5 or 0.8	0.5 or 0.8	0.5 or 0.8
Purified water	100% Q.S.	100% Q.S.	100% Q.S.	100% Q.S.	100% Q.S.	100% Q.S.

DOE application

The use of DOE is well established for determining method robustness, such as how much the mobile-phase composition, column temperature, and flow rate can vary. DOE is also well used in formulation screening. This approach broadens DOE to include method validation over a range of formulations.

QbD application

The MVbD approach applies to these QbD principles:

- *Risk management assessment* of the potential critical validation parameters. Systematic analysis (e.g., fishbone diagram) is done based on historical knowledge. The QbD/DOE output confirms those that are critical.
- *Analytical target profile (ATP).* Once the required process capability is known, the required method accuracy and precision acceptance criteria are defined in the ATP.
- *Control strategy.* DOE output defines those parameters that have the most impact on the method performance. Monitoring these parameters throughout development will help define acceptable ranges.
- *Continuous improvement.* MVbD provides the acceptance criteria that must be met to move to new technologies.
- *Knowledge management.* Knowledge gained is cycled backed to accelerate the next program.

Traditional versus DOE approaches

Traditionally, each new drug-product formulation requires validation to support clinical testing. In early development, the method is validated for linearity, accuracy, and precision. Method linearity is determined across five concentrations from 50% to 150% of the nominal (100%) concentrations. Accuracy and precision can be combined with the linearity study by doing six replicates at the 100% (nominal) concentration and three replicates at the other concentrations (50%, 75%, 125%, and 150%), which gives a total of 18 sample preparations. If there are five new formulations during development that require separate validation, a total of 90 sample preparations would be needed. This approach is resource intensive and affects project timelines. In this given example, only one formulation component is varied. As more components are varied, the workload increases proportionally.

The challenge with this approach is:

- It does not statistically define a design space
- It does not employ QbD principles.

A QbD/DOE approach validates a method over a range of formulations within a defined design space. Movement within this design space does not require method revalidation with each new formulation. The DOE approach detects any excipient–API interactions and critical validation control parameters.

A DOE approach is not necessarily more labor intensive than the traditional method-validation approach and additional information gained is well worth the exercise. As described, the traditional approach requires at least 90 sample preparations to validate five formulations over the course of the development. Using DOE to validate across a broader range that includes these five formulations would require only three determinations for each of the five formulations, resulting in a total of 15 sample preparations.

Steps to perform a MVbD

- *Step 1: Define the range of formulations and required process capability.* A formulation screening DOE may be used to determine all possible clinical formulations for the study. Manufacturing process capabilities need to be considered to define the ATP (i.e., the necessary accuracy and precision to ensure acceptable data). Full factorial, fractional factorial and/or custom (d-optimal) design all may be used in developing the study design.
- *Step 2: High-performance liquid chromatography (HPLC) method selection.* A method should be developed such that sample preparations of the different formulation can be diluted to the same API concentrations. The diluted sample from each formulation is injected onto the HPLC column under the same chromatography conditions. Standardizing these conditions will facilitate DOE and latter method-robustness studies.
- *Step 3: DOE design.* The set up of the DOE can be accomplished with or without using DOE software. Inputs to the DOE include a number of varying factors, such as the different API levels and/or excipient and preservative levels.
- *Step 4: ICH statistics and design space.* Data are analyzed for linearity, precision, and accuracy, including confidence intervals. Any interactions are reported and a design space

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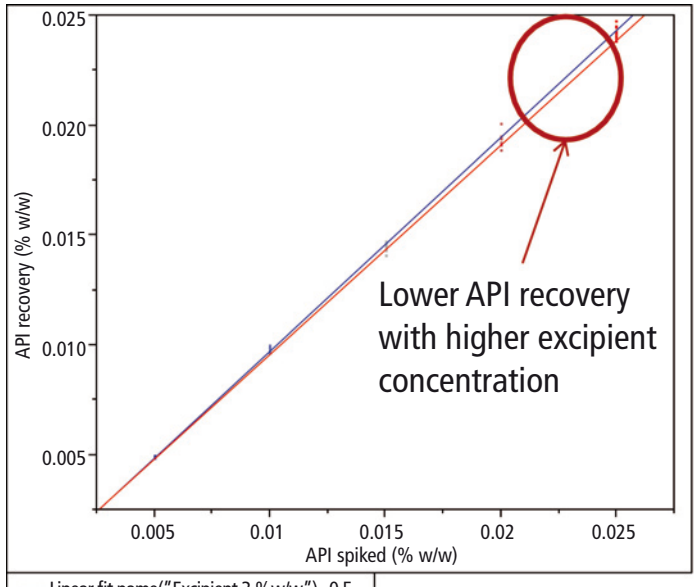
Figure 1: A design-of-experiment (DOE) approach for three factors showing the DOE pattern, API, preservative, Excipient 3 spiked concentrations along with simulated percent recovery data.

	Pattern	API w/w%	Preservative w/w%	Excipient 3 w/w%	Percent recovery
2	1---	0.005	0.01	0.5	98.0
3	1---	0.005	0.01	0.5	97.7
4	1--+	0.005	0.01	0.8	95.6
5	1--+	0.005	0.01	0.8	96.2
6	1--+	0.005	0.01	0.8	96.6
7	1+--	0.005	0.03	0.5	97.4
8	1+--	0.005	0.03	0.5	97.1
9	1+--	0.005	0.03	0.5	97.8
10	1++	0.005	0.03	0.8	96.2
11	1++	0.005	0.03	0.8	96.6
12	1++	0.005	0.03	0.8	96.0
13	2---	0.01	0.01	0.5	99.6
14	2---	0.01	0.01	0.5	98.4
15	2---	0.01	0.01	0.5	97.6
16	2--+	0.01	0.01	0.8	96.3
17	2--+	0.01	0.01	0.8	95.7
18	2--+	0.01	0.01	0.8	97.4
19	2+--	0.01	0.03	0.5	97.4
20	2+--	0.01	0.03	0.5	97.2
21	2+--	0.01	0.03	0.5	97.3
22	2++	0.01	0.03	0.8	96.0
23	2++	0.01	0.03	0.8	96.9
24	2++	0.01	0.03	0.8	95.9
25	3---	0.015	0.01	0.5	95.5
26	3---	0.015	0.01	0.5	96.0
27	3---	0.015	0.01	0.5	96.5
28	3--+	0.015	0.01	0.8	93.5
29	3--+	0.015	0.01	0.8	96.8
30	3--+	0.015	0.01	0.8	95.8
31	3+--	0.015	0.03	0.5	96.6
32	3+--	0.015	0.03	0.5	97.6
33	3+--	0.015	0.03	0.5	97.1
34	3++	0.015	0.03	0.8	96.2
35	3++	0.015	0.03	0.8	95.6
36	3++	0.015	0.03	0.8	95.2
37	4---	0.02	0.01	0.5	100.2
38	4---	0.02	0.01	0.5	97.4
39	4---	0.02	0.01	0.5	96.9
40	4--+	0.02	0.01	0.8	94.1
41	4--+	0.02	0.01	0.8	95.2
42	4--+	0.02	0.01	0.8	95.2
43	4+--	0.02	0.03	0.5	96.7
44	4+--	0.02	0.03	0.5	97.2
45	4+--	0.02	0.03	0.5	96.6
46	4++	0.02	0.03	0.8	96.0
47	4++	0.02	0.03	0.8	95.8
48	4++	0.02	0.03	0.8	95.6
49	5---	0.025	0.01	0.5	98.9
50	5---	0.025	0.01	0.5	96.8
51	5---	0.025	0.01	0.5	96.6
52	5--+	0.025	0.01	0.8	95.6
53	5--+	0.025	0.01	0.8	95.8
54	5--+	0.025	0.01	0.8	95.2
55	5+--	0.025	0.03	0.5	97.9
56	5+--	0.025	0.03	0.5	97.0
57	5+--	0.025	0.03	0.5	97.6
58	5++	0.025	0.03	0.8	96.2
59	5++	0.025	0.03	0.8	95.6
60	5++	0.025	0.03	0.8	95.8

Figure 2: Linearity data for API recovered versus API spiked for formulations containing 0.05% and 0.08% (w/w) levels of Excipient 3.



Linear fit name("Excipient 3 %w/w")=0.5

API recovery (%w/w) = -6.117 e-6 + 0.9739133*API spiked (% w/w)

Summary of fit

RSquare	0.999422
RSquare adjusted	0.999401
Root mean squre error (RSME)	0.000171
Mean of response	0.014603
Observations (or sum of weights)	30

RSME used to set specifications

is defined. The design space is defined by fitting a model to the factors used in the evaluation of assay concentrations and other key factors that may interfere or influence assay precision or bias. After fitting the model, the design space may be visualized using contour plot or profilers.

Case study

To illustrate the MVbD process, a simulated case study is presented where three factors are varied over a range of formulations (see **Table I**). The API concentrations are varied from 0.005%, 0.01%, 0.015%, 0.02%, and 0.025% (w/w). Preservative concentrations are either 0.01% or 0.03% (w/w) and concentrations of Excipient 3 are either 0.5% or 0.8% (w/w).

The DOE design is shown in **Figure 1**. The DOE pattern is presented as 1, 2, 3, 4 or 5 --, -+, +- or ++. The numbers 1 through 5 represent the five API concentrations and the "+" or "–" represent with or without the two possible preservative and excipient concentrations. Three replicates are done for each combination of API, preservative, and excipient concentration. A total of 60 sample preparations is required. The DOE typically suggests a randomized sample preparation to avoid any sample preparation variability; however, because the variability is low, a standard sample-preparation scheme can be followed.

Figure 1 also presents the percent recovery data. The required ICH statistics can be obtained from these data. For example, **Figure 2** shows linearity data along with typical linearity statistics. One key output is the root mean square error (RMSE); this parameter identifies method variability that is critical for understanding the method contribution to the overall process variability.

Figure 2 also shows linearity plots of percent recovery versus the two excipient concentrations. The difference in slopes indicates interaction (i.e., a lower API recovery at a higher level of Excipient 3 concentration), possibly due to interaction of the excipient with the API. Such information is important for the formulator and method developer to consider if higher preservative levels are needed.

Figure 3 presents the mean percent recovery for each combination of API, preservative, and excipient along with the corresponding confidence limits. In the

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example describe, there was a somewhat lower API recovery with the higher excipient levels, which is further illustrated in **Figure 4** as discussed in the following.

Design space. A design space is illustrated in **Figure 4**. It is obtained by mathematically modeling the primary main effects and secondary two-factor interactions as well as possible polynomials using a DOE software. The operating range is the white space shown in **Figure 4**; it is where the method accuracy and precision meet the acceptance criteria. Adding formulations outside this range would require confirmatory testing.

System linearity, quantitation limits (QL), and detection limits (DL). To ensure the sample amount injected is within the linear range of the detector, a separate experiment can be done where the sample concentration is varied from 50% to 150% of the nominal (100%) concentration. If the potency method is also used to quantitate impurities, a wider linearity study can be performed from 100% to 0.03%. The QL and DL for the impurities can be determined by the ratio of RMSE to the slope, as described in ICH Q2 (R1).

Figure 3: Accuracy data with confidence intervals for varied levels of API, preservative and Excipient 3.

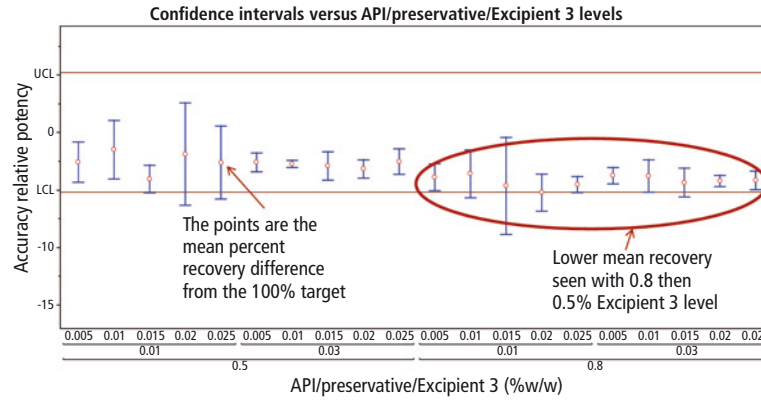
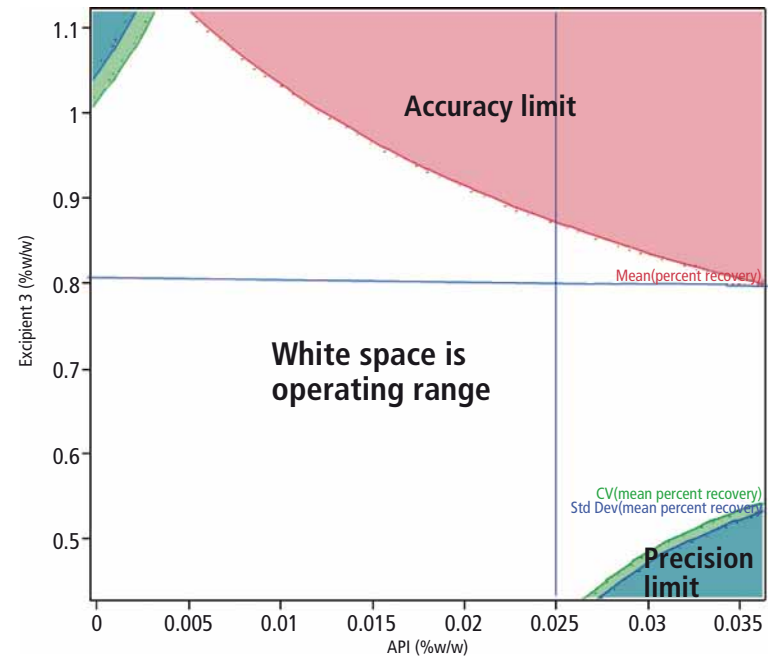


Figure 4: Design Space from the three-factor case study, API percent recovered versus the amount of Excipient 3 in the formulation.



Other MVbD outcomes

Control strategy. Figure 4 shows there is less precision (i.e., higher standard deviation and confidence values) at the higher API levels for lower amounts of Excipient 3. This lower precision is approaching the acceptance limit. Similarly, accuracy is approaching the acceptance limit as the excipient and API levels increase. These parameters need to be monitored in case the method needs to be optimized prior to transfer to the final manufacturing site(s).

Continuous improvement. The contour profiler (top graph) in **Figure 5** shows a graph of the balance between precision and bias and its influence on product acceptance/failure rates based on the DOE data. Combinations of method precision and bias must fall within the designated white space to meet the acceptance criteria. The equation for how precision and bias influence product acceptance rates is as follows:

$$1-\text{Normal Distribution}\left[\frac{[LSL-[Bias+\text{Nominal}]]}{\text{Precision}}\right]-\left[1-\text{Normal Distribution}\left[\frac{[USL-[Bias+\text{Nominal}]]}{\text{Precision}}\right]\right]$$

LSL = lower acceptance criteria, USL = upper acceptance criteria, bias = mean percent recovery - 100%, nominal = 100%, and precision = mean standard deviation.

The prediction profiler (bottom graphs) in **Figure 5** allows the precision and bias to be varied to determine the impact on % acceptance rates. This tool can be used to justify moving to new technologies and new specifications by showing that the acceptance criteria will still be met.

Knowledge management. The lower recovery of API observed at high levels of excipient concentrations adds to the formulator's knowledge base. If higher excipient concentrations are needed in future formulations, this aspect needs to be considered.

Regulatory strategy and potential hurdles

Since the MVbD approach is not specified in ICH regulations, not all regulatory agencies may accept this approach. Some filing strategies are briefly discussed.

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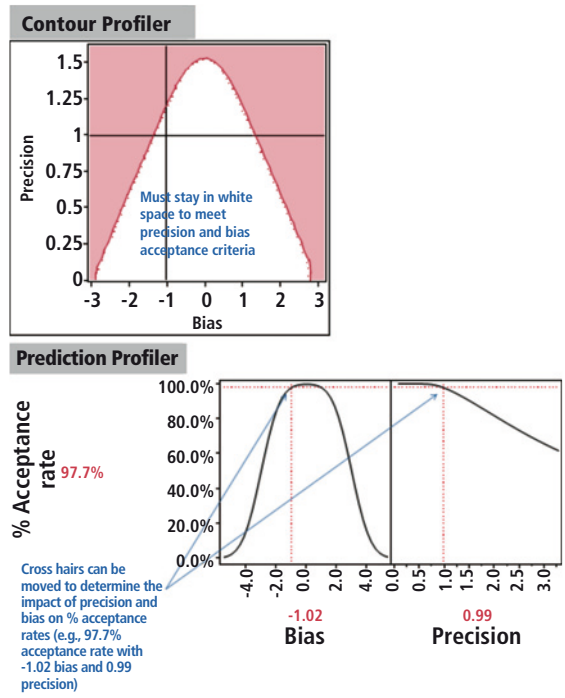
Figure 5: The top contour profile is a plot of precision (mean standard deviation) versus bias (mean percent recovery – 100%). Any combination of precision and bias that falls in the white space will give acceptable results. The bottom prediction profiler is a tool where bias and precision can be varied by moving the cross hairs to determine the impact on % acceptance rate.



- **US:** The MVbD approach can be presented in an investigational new drug (IND) application and discussed at the end of Phase II chemistry, manufacturing, and controls (CMC) meeting. The details can be present in a MVbD design protocol along with a rationale for moving within the design space without revalidation. Moving outside the design space could be justified through the use of comparability protocol.
- **EMA and the rest of the world:** Submission of the MVbD rationale, justification, and protocol early in the development process is warranted since a face-to-face conversation may not be possible. Alternatively, this information can be supplied when responding to any agency questions.

Conclusions

The MVbD approach is statistically rigorous and scientifically defensible. It is in line with current regulatory thinking and allows movement to new formulations within the design space without revalidation. The MVbD approach provides a better understanding of the critical parameters of a method and allows greater flexibility and speed during formulation development, especially when time and resource are under constraints. Through judicious planning, MVbD can encompass early formulation design efforts so that a wide range of formulations can be used to define the method-validation design space. Once the ATP has been defined, movement to new analytical technologies and formulations is justified as long as the ATP criteria are met. This approach enables continuous improvement for efficiency and quality gains.

Control strategy, knowledge management, and measurement uncertainty are other key MVbD outputs. The DOE identifies critical validation parameters to monitor and control. The DOE also adds to the knowledge base that will help accelerate future programs. Knowing the method contribution to overall process variability enables setting appropriate in-process controls and product specifications.

Internal company alignment is needed to support a MVbD approach and define a global filing strategy. Early discussions and a presentation of a MVbD protocol to regulatory agencies can help avoid questions during regulatory submission review.

Additional studies can be done to expand the design space but not all changes may require additional studies, for example:

- Changing a grade or source of excipient (e.g., from one grade of lactose to another)
- Using a similar excipient
- Different drug substance process.

Some of these and other changes may be justified based on the degree of interactions seen from the DOE data. For example, a source change in lactose may be justified if there are no interactions seen at higher lactose concentrations and historical data on other formulations has shown no impact.

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Miniaturization of a Simulated Gastric Fluid Dispersion Experiment On a Microfluidics System

Nicole L. Hill, Todd Nelson, Elizabeth Kwong, Tim Rhodes, Brian Farrer, and Allen Templeton

Formulations for preclinical safety assessment studies are often prescreened by formulation scientists *in vitro* prior to use in animal models. By simulating the precipitation characteristics of a formulation in biorelevant media, the performance of a formulation can be predicted. The predictability depends on the sensitivity of detection and simulation of the mixing of the vehicle and biorelevant media. The authors describe the miniaturization of these types of experiments using a microfluidic chip system, combined with detection by optical microscopy. The results show the potential of microfluidics as a tool to help reduce compound requirements, time, and costs in formulation development.

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Dispersion experiments are heavily used in the pharmaceutical industry to screen potential oral formulations *in vitro.* The studies are run to rank how several formulations will perform prior to dosing new chemical entities *in vivo*. The experiment intends to mimic what occurs as the formulations are dosed orally and traverse through the gastrointestinal tract (1, 2). This experiment also is used to understand the mechanism of variability upon oral dosing. As a result, compound and animal resources can be spared when failed formulations are not pursued in actual animal studies. This experiment is particularly useful in drug discovery and development by saving time and resources while still advancing drug candidates.

Microfluidic systems

Microfluidic systems are evolving as useful tools for miniaturizing a variety of standard laboratory experiments (3). Many industries are using such systems, and more recently, the pharmaceutical industry is taking note (4). There are applications for microfluidics across the pharmaceutical industry ranging from scaling down the synthesis of challenging molecules to evaluating the effects of new chemical entities on biological systems (5).

Microfluidic systems are of particular interest to the pharmaceutical sciences as tools for formulation development. Emulsion-based formulations are highly prevalent in the industry. Okushima et al. demonstrated that monodispersed double emulsions could successfully be generated with tunable control over the size and number of internal droplets produced (6). In this example, a specialized chip with hydrophobic and hydrophillic junctions was used to generate the various double emulsions.

Liposomes also have been of interest to formulation scientists for several decades (7). Jahn et al. demonstrated the successful generation of liposomes on a microfluidics device (8). The liposomes generated were monodispersed, and the size of the particles was controlled by varying the flow rate. The mixing capabilities of the chip allowed liposomes to self-assemble in the channel, which would also allow for drug encapsulation and ultimately liposomal formulation preparation.

Both of these studies used droplet-based microfluidics. The liposome-generation example used the microfluidic technique of hydrodynamic focusing, and the double-emulsion example


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used T-junction droplet generation (9). With respect to droplet microfluidics, the methods are complementary. In general, droplet-based microfluidic systems have the advantage of creating separated droplets that distinguish small amounts of reagents (10). T-junction droplet-generation systems are particularly flexible as several T-junctions can be placed in tandem, thereby allowing sequential reactions or mixing opportunities to occur.

This article describes the use of a T-junction droplet microfluidics system to evaluate oral formulations of select model compounds by executing a simulated gastric fluid (SGF) redispersibility experiment directly on a microfluidics chip. This article describes preliminary proof-of-concept experiments. Morever, the results show the potential to save significant amounts of compound, animal resources, time, and cost in developing formulations for new chemical entities.

Experimental

The following materials were used in the study: naproxen (Chemical Abstracts Service [CAS] Number 22204-53-1, Sigma-Aldrich); naphthol (CAS Number 90-15-3, Sigma-Aldrich); perfluorodecalin (PFD) (CAS Number 306-94-5, Acros Organics), polyethylene glycol 400 (PEG 400, CAS Number 25322-68-3, Sigma Aldrich; Imwitor 742 (Sasol), and polysorbate 80 (CAS Number 9005-65-6, Tween 80, Fisher Scientific.

Formulations were prepared at 50 mg/g concentration representing a 100 mg/kg dose *in vivo* when PEG 400 is dosed at 2 mL/kg. Model compounds naproxen and naphthol were fully solubilized at this concentration. In addition, naphthol was prepared at 100 mg/g in 1:1 Imwitor 742:Tween 80. The compound also was fully solubilized. SGF was prepared by dissolving 2.0 g of sodium chloride (NaCl) in 1 L of deionized water and adjusting the pH to 1.2 with 1 N HCl (hydrochloride acid).

The microfluidics system was from Dolomite Microfluidics, and the experiments were run on a standard quartz T-junction chip with a channel size of 190 µm. The reagents were fed into the chip using three Dolomite Mitos Pressure Pumps (P-Pumps) with the pressure attenuated based on the viscosity of the liquids. The experiments were run at room temperature. After the experiments were completed, the chips were disassembled and transferred to either a Zeiss Axiovert 200M inverted microscope or a Nikon Eclipse E800 microscope, both equipped with a polarizing light filter to assess crystallinity.

Results and discussion

The microfluidic system used for this study was the Dolomite pressure-based droplet microfluidics system. The experiment required three Mitos-P pumps with one equipped with a three-way outlet head. A standard quartz channel chip was used, which was optically transparent and stable to organic reagents. **Figure 1** shows an image of the chip relative in size to a penny and also the schematic representation that is used throughout this article. In the T-junction schematic, the phase coming through Channel B would be considered the "dispersed" phase that would be dispersed within the "continuous" phase flowing though Channels A and C. The lines are supplied by the Dolomite P pumps, with the pressures adapted to the individual viscosity of each liquid and until suitable droplet size is achieved (droplets of B within the carrier fluid channeled through Channels A and C).

The goal of these experiments was to see whether a typical redispersibility experiment could be performed on a droplet-generating microfluidics system. The redispersibility experiment involves preparing a formulation, either

Figure 1: Quartz microfluidic channel chip used in experiments as compared to the size relative to a penny and the schematic representation of the chip (top) and the naproxen formulation in polyethylene glycol 400 (PEG 400) dispersed as a plug in the carrier fluid perfluorodecalin (PFD) (bottom). The plug is optically distinguishable from the carrier fluid and also traveled freely through the channel.

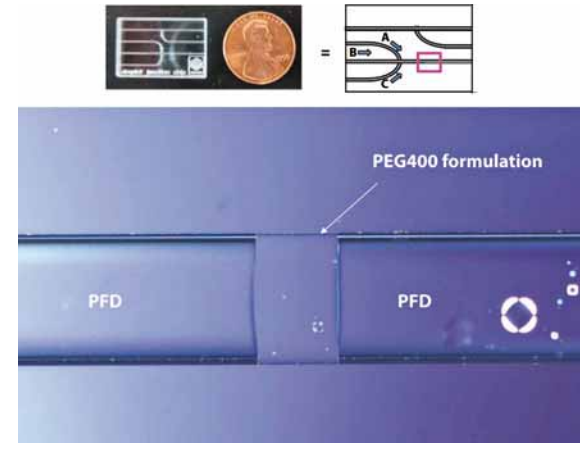

Figure 2: Benchtop-dispersed droplets of a naproxen/polyethylene glycol 400 (PEG 400) formulation in simulated gastric fluid within the microfluidics chip channel separated with the perfluorodecalin carrier fluid. The image was taken under polarized light.

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Figure 3 (a): Schematic representation of the dispersion experiment plan. The yellow channel represents the simulated gastric fluid (SGF); the pink channel the naproxen dissolved in polyethylene glycol 400 (PEG 400); and the grey channel the perfluorodecalin (PFD) carrier fluid. Figure 3(b) is the schematic representation of the second dispersion experiment plan. The SGF droplets were created first and subsequently mixed with the formulation. The yellow channel represents the SGF; the pink channel the naproxen dissolved in PEG 400; and the grey channel the PFD carrier fluid.

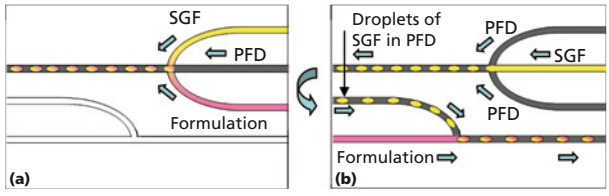
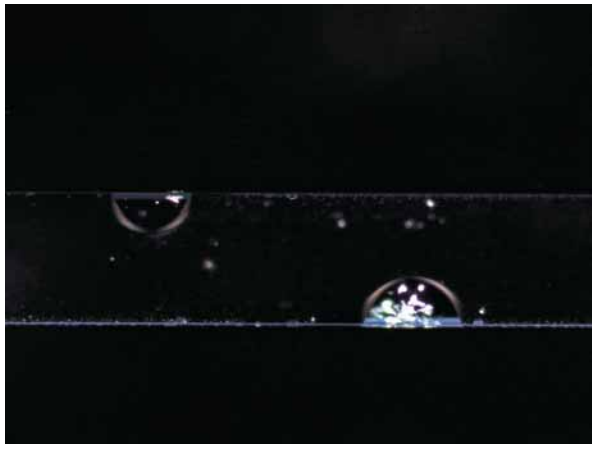


Figure 4. Droplets of the naproxen/polyethylene glycol 400 (PEG 400) formulation dispersed in simulated gastric fluid directly within the microfluidics chip channel, separated with the perfluorodecalin carrier fluid. The image was taken under polarized light.



solution- or suspension-based, of a new chemical entity in a dosing vehicle and then dispersing the formulation into a biorelevant medium. Potential outcomes include the compound crashing out as either crystalline or amorphous physical phase or the compound remaining completely solubilized. If the starting formulation is a solution, when the compound of interest precipitates from the formulation vehicle, it is considered a less favorable formulation as this will render the active compound less absorbable in the intestinal barrier.

The initial experiment performed was to generate a plug of a solution formulation of naproxen dissolved in PEG 400 within the carrier fluid, PFD, to verify that the viscous PEG 400 would travel through the channel of the chip, which proved successful (see **Figure 1**). PFD was chosen because as a fluorocarbon, it is immiscible with PEG 400 and the aqueous-based SGF. In this experiment, the carrier fluid was plumbed through Channels A and C as depicted in **Figure 1,** and the naproxen/PEG 400 formulation was brought in through Channel B. The naproxen/PEG 400 formulation was successfully "plugged" in the PFD carrier fluid and was visually distinct and traveled easily through the microfluidic channel.

Next, the same naproxen in the PEG 400 formulation was dispersed into SGF on the benchtop, and the resulting suspension was plumbed through the chip. The experimental design was the same in that Channels A and C were the PFD carrier fluid and Channel B was the suspension of the naproxen formulation dispersed (on the benchtop) in SGF. This experiment verified that plugs of a formulation suspension could travel through the channel of the chip. For visualization, the chip was removed from the microfluidics chip-holder system and examined with polarized light microscopy. The characteristic birefringence was observed through the quartz chip, suggesting that the naproxen precipitates from the PEG 400 as crystalline material (see **Figure 2**).

Dispersing the naproxen in PEG 400 formulation into SGF directly on the microfluidic chip was attempted next. The design of the experiment is outlined in **Figure 3(a)**. The naproxen in PEG 400 formulation (see **pink channel, Figure 3 [a])**, SGF (see **yellow channel, Figure 3 [a])**, and carrier fluid (PFD, see **grey channel**, **Figure 3 [a])** were plumbed into three separate lines with the intention of generating droplets of dispersed formulation in SGF separated by the carrier fluid at the junction of the chip. This experiment was somewhat unsuccessful as the high viscosity of the PEG 400 formulation line caused significant backflow issues. The formulation precipitated; however, there was no controlled droplet generation. Looking at the chip under polarized light indicates the naproxen/PEG 400 formulation crashed out of solution generating a crystalline precipitate, which was a promising result; however, more control was desired.

To achieve more control over the redispersibility experiment, the experimental design was changed. In the new experiment, SGF droplets (see **yellow channel, Figure 3 [b])** were first generated in the carrier fluid [see **grey channels Figure 3 [b]**) and as they exited the chip, the exit line of tubing was replumbed into one of the bottom channels of the microfluidics chip. The second of the lower channels of the chip was plumbed with the naproxen in the PEG 400 formulation (see **pink channel, Figure 3[b]**). This experiment proved successful as once the formulation was dispersed into the SGF droplets, the new combined droplets continued to travel through the channel. In addition, the timescale was appropriate to observe the precipitation of the naproxen into crystalline material before the newly formed droplets exited the chip (see **Figure 4)**.

Having demonstrated that it is possible to perform a redispersibility experiment within a microfluidic chip, the final experiment aimed to differentiate between different formulations of a model compound. In this case,

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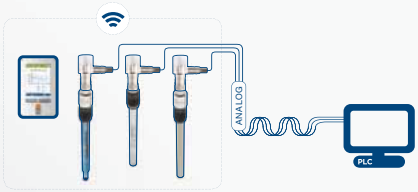

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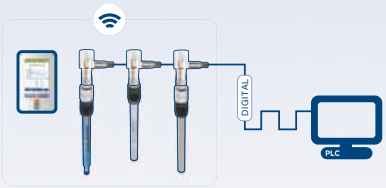

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formulations of naphthol were prepared at 50 mg/g in PEG 400 and 100 mg/g in Imwitor 742:Tween 80. The difference in concentrations of these two formulations represents the difference in dosing volumes for the vehicles when administered at the same dose. The design of these experiments follows the schematic detailed in **Figure 3(b)**. The naphthol formulation in PEG 400 was dispersed first. As the formulation mixed with the SGF droplets and traveled through the channel, there was no precipitation event (data not shown).

Imwitor 742:Tween 80 is a known self-emulsifying drug-delivery system (SEDDS) (11). SEDDS vehicles are typically comprised of oils and surfactants and solubilize highly lipophilic compounds. Upon reaching the aqueous environment of the stomach, the vehicle creates emulsions, which often boost *in vivo* exposure. When this formulation of naphthol was mixed with SGF droplets at the T-junction, the emulsifying nature of the vehicle was observed. This emulsion property is particularly evident when viewed under nonpolarized light (see **Figure 5 inset**). When viewed with the polarizing filter on the microscope, it is clear that the naphthol compound was precipitating out as evidenced by the birefringence observed at the interface of the two solutions. The precipitation, however, was somewhat impeded by the emulsification of the Imwitor 742:Tween 80 vehicle, and no distinct crystal habit was formed (see **Figure 5**).

Having shown it was possible to disperse a formulation in SGF on a chip, a comparison experiment was conducted examining how the same formulations behave when dispersed in SGF on the benchtop. Standard SGF dispersion experiments were set up where the solution formulations of naphthol in PEG 400 and naphthol in Imwitor 742:Tween 80 [1:1] were dispersed into SGF at a ratio of 1:1. These experiments were run in small scintillation vials equipped with stirbars. **Figure 6** shows the formulation vials prior to and after SGF dispersion. The results of the traditional benchtop SGF dispersion experiment parallel what was observed in the microfluidic dispersion experiments. Upon dispersion into SGF, the naphthol in PEG 400 formulation remained a solution, and the naphthol in Imwitor 742:Tween 80 [1:1] formulation became cloudy.

Figure 5: Dispersion of the naphthol/Imwitor 742:Tween 80 formulation dispersed in simulated gastric fluid directly within the microfluidic chip channel. The image was taken under polarized light. Inset: nonpolarized light image.

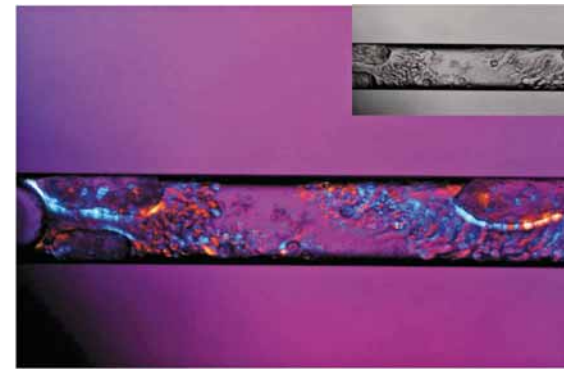
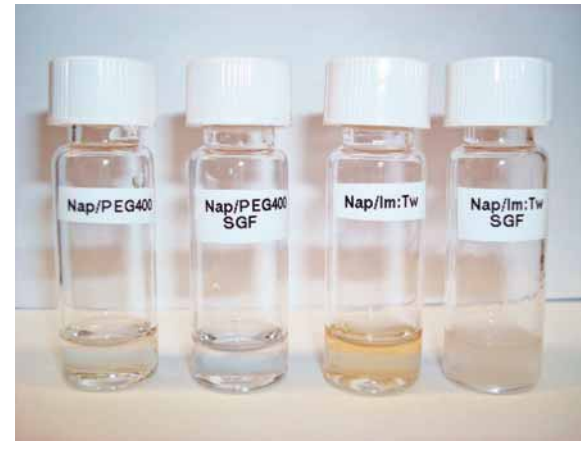


Figure 6: Naphthol/polyethylene glycol 400 (PEG 400) formulation before and after dispersion into simulated gastric fluid (SGF) and naphthol/Imwitor 742:Tween 80 [1:1] formulation before and after dispersion into SGF.



Conclusion

These experiments demonstrate the proof of concept that a dispersion experiment can be performed within a T-junction microfluidics chip system. When individual droplets of SGF were mixed with formulations at the T-junction, the model compounds either stayed in solution or precipitated out. When the compounds did precipitate out, information about the physical form of the precipitated chemical entity was obtained as the microfluidic chip is visualized under polarized light microscopy.

As there are significant benefits, scaling down redispersibility experiments also was explored by other groups. Dai and Mansky (12, 13) describe a method using a 96-well plate that uses a small amount of compound to screen the solubilizing effect of several excipients once dispersed into simulated intestinal fluid [SIF]. The method is further validated by comparing the results of the miniaturized experiments to traditional formulation dissolution testing and actual *in vivo* studies (14). In addition, Gopinathan et al. (15) developed a 96-well plate based high-throughput formulation screening strategy. The company TransForm (16, 17) has developed similar high-throughput formulations screens, even extending to a 384-well plate. For these examples, the reagents are mixed by vortexing or sonicating the plate, or in some cases, heating to solubilize the initial compound. These examples illustrate the direction the pharmaceutical industry is headed with respect to formulation screening in the discovery space: using small amounts of compound to evaluate many different formulations. The experiments detailed in this article are complementary as they use microfluidic technology,

specifically T-junction droplet generation. Although not as developed as the aforementioned examples, this method offers the potential benefit of *in situ* mixing that droplet microfluidics offers (18, 19). This feature would be beneficial when highly viscous formulations are evaluated and may be a better representation of how formulations are dynamically mixed in the gastrointestinal tract. Further, microfluidic technology has the potential to consume even less compound than what would be used in a 384-well plate experiment.

Future experiments under consideration by the authors include a two-step SGF and fasted state SIF redispersibility study that would more closely mimic the transport of a compound from the acidic environment of the stomach to the more neutral pH (i.e., pH 6.5) of the small intestine. In addition, the system can be temperature-controlled, and the effect of temperature on these types of experiments may be explored.

In summary, scaling down redispersibility experiments to the microfluidic scale has the potential to have significant impact on how formulations are screened in the pharmacuetical industry. Performing redispersibility experiments on a much smaller scale allows more formulations to be screened *in vitro* using less material. When combined with more powerful detection techniques, the experiment also can provide more understanding of the behavior of the physical phase in the gastrointestinal environment. This information can help formulation development scientists identify and understand the most effective formulations for future *in vivo* experiments more efficiently.

Acknowledgement

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Trends in safe handling of
POTENT COMPOUNDS
in pharmaceutical manufacturing processes

LIVE WEBCAST: Wednesday, May 15, 2013 at 11:00 AM EDT

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EVENT OVERVIEW:

In the pharmaceutical industry, an increasing number of new drug candidates are considered "highly potent", which can have significant impact on how they can be safely handled in drug product development and manufacturing. This webcast explores what the term "highly potent" means and discusses what is required to manufacture these drugs from an equipment containment perspective. The main focus will be on the safe handling of these drugs (e.g. safety of equipment operators). However, these principles also apply to meeting Good Manufacturing Practices (GMP) requirements for minimizing cross-contamination to other drugs manufactured in the same facility. The use of control banding, a procedure for assigning an active pharmaceutical ingredient to a potent or non-potent hazard category corresponding to an airborne concentration range, will also be discussed. Two case studies that are designed to highlight the key take home messages of this session will be presented.

Key Learning Objectives:

- Defining the term "highly potent"
- Requirements to manufacture high potent drugs from an equipment containment perspective
- Safe handling of highly potent drugs while meeting GMP requirements
- The use of control banding

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Fixed-Oil Excipient Monographs

Development of USP Fixed-Oil Reference Standards

Hong Wang, Catherine Sheehan, Lawrence H. Block,
Richard C. Moreton, Richard H. Wendt, Shireesh P. Apte, and Eric J. Munson

This article summarizes the development and modernization of the *United States Pharmacopeia–National Formulary* (*USP–NF*) fixed-oil excipient monographs. Fats and fixed oils are processed from natural sources and have complex chemical compositions. As part of the public standards-setting processes, USP staff and the Excipients Expert Committee have formulated a strategic analytical testing plan for fixed oil excipients. The plan balances modernization with ease of adoption and method simplicity. Modernization introduces more specific compositional methods that can identify as well as quantify the analyte(s) of interest. A combination of simple orthogonal methods uses existing instrumentation that can be applied to a multitude of fixed-oil monographs and encourages ease of adoption. This plan also has helped make possible the development of USP Reference Standards for such complex excipients because the proposed analytical methods provide a comprehensive understanding and characterization of fixed oils. An extended version of this article is available at www.PharmTech.com/USPfixedoil.

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The US Pharmacopeia (USP) Monographs—Excipients Expert Committee (EXC EC) for the current 2010–2015 revision cycle is responsible for the 31 *United States Pharmacopeia–National Formulary* (*USP–NF*) monographs with "oil" in the monograph title (see **Table I**) in *USP 35–NF 30* through the Second Supplement (1). The 31 oil excipients include vegetable oils (edible), petrochemical oils, and essential oils. All vegetable oils are termed "fixed oils" in *USP–NF*. The term *fixed oils* distinguishes them from the relatively volatile petrochemical oils and essential oils. Fixed oils are obtained by expression or extraction. Their consistency varies with temperature: some are liquid (oils), others are semisolid (fats), and still others are solid (tallows) at ambient temperature. Most fixed-oil excipients included in *USP–NF* are refined oils.

Twenty-four of the 31 *USP–NF* oil excipients are fixed oils or fixed oil derivatives. Most fixed oils consist mainly of triglycerides (or triacylglycerols). The four *USP–NF* mineral oils in **Table I** are classified as petrochemical oils: each is defined as a purified mixture of liquid hydrocarbons obtained from petroleum. The three volatile essential oils (see **Table I**) are composed primarily of acyclic monoterpenoids, terpenes and their derivatives, or aromatic compounds and their derivatives, and contain lesser quantities of alcohols, aldehydes, esters, and/or phenols.

Three of the 22 *USP–NF* fixed oils—castor oil, soybean oil, and safflower oil—are designated as *USP*, and the remaining fixed oils are designated as *NF*. The *USP–NF* fixed oils can have different functions. The majority are used as oleaginous vehicles or solvents in drug formulations. However, some are used as emulsifying agents, flavors and perfumes, ointment bases, plasticizers, stiffening agents, tablet or capsule lubricants, wetting or solubilizing agents, or coating agents.

Need for modernization

Monograph test deficiencies before modernization. Incidences of intentional adulteration have increased in recent years, and adulteration has become a major concern as supply chains continue to expand globally. Intentional adulteration can include the dilution of expensive fixed oil products with cheaper substances. Compendial standards in existence for a long period of time may require updates to keep pace with current regulatory and safety requirements and to incorpo-

rate advances in analytical methodology and metrological science (2).

Further, substances derived from natural sources historically were characterized mostly from a safety perspective using generally applicable but nonspecific tests to detect elemental impurities, residual process impurities, and pesticides. Because of the deficiencies in these fixed-oil excipient monographs (see **Table I**), users were unable to relate the material's chemical composition to its physical and chemical properties or to anticipate any potential degradation or decomposition during storage. A majority of the oil monographs, including petrochemical oil and essential oil monographs in *USP 28–NF 23* (2005) did not contain identification tests and thus would conform with difficulty to current GMPs (3).

In fixed-oil excipient monographs before modernization, most procedures for testing fixed-oil substitutes were wet chemistry–based methods with undefined or poor sensitivity and specificity (e.g., color reactions caused by the presence of particular nonfat ingredients). Therefore, it was desirable to replace these wet chemistry tests with tests that could detect specific adulterants or contaminants. Incorporating such tests in *USP–NF* fixed-oil monographs could help ensure the authenticity of the fixed oils. Most importantly, monograph modernization should introduce tests to determine fixed oil chemical composition specifications.

The development of *USP* general chapters to characterize fixed oils

***USP* General Chapter Fats and Fixed Oils <401>.** USP General Chapter Fats and Fixed Oils <401> includes several test procedures to characterize and determine the properties of fats and fixed oils. Before its proposed revision that appeared in 2008, the chapter contained mostly simple wet chemistry–based methods to measure values characteristic of fats and fixed oils such as acid value (free fatty acids), ester value, hydroxyl value, iodine value, and saponification value (4). Essentially, these tests used chemical reactions to quantitatively estimate the selected functional group(s) or to calculate—but not necessarily to identify—the constituents of a fat or oil. Thus, ester value, hydroxyl value, iodine value, and saponification value tests traditionally are treated as oil and fat structure index tests. These indices, especially if combined, help to provide a rough idea of the identity of the sample. A triglyceride can be hydrolyzed to fatty acids and glycerin. Thus, the acid value (free fatty acids) test is used as a measure of the degree of an oil's hydrolysis.

In addition, peroxide value, anisidine value, and total oxidation value (totox) tests also were included in general chapter <401> before the 2008 revision (4). The tests for anisidine value and total oxidation value (totox) were proposed in 2003 to support several monographs that contain polyunsaturated fatty acids, particularly some dietary supplement monographs (5). Fats and oils containing unsaturated fatty acids are prone to oxidation. Peroxide value, anisidine value, and total oxidation value (totox) tests using wet chemistry principles can reveal the extent of oxidative degradation of fats and fixed oils. Peroxide value measures the amount of primary oxidation products such as hydroperoxides, and the anisidine value measures secondary products including aldehydes and ketones. Because the tests can determine the extent of oxidative deterioration, they are useful analytical tools to predict the expected shelf life of a fat or oil and to monitor an oil's stability.

Before the proposed revision in 2008, <401> also provided tests for unsaponifiable matter, solidification temperature of fatty acids, and fatty acid composition (4). The latter employs a modern gas chromatographic (GC) test procedure to analyze the distribution of fatty acid moieties that are attached to the three hydroxyl groups of the glycerin backbone if the sample is a fat or fixed oil. Fatty acid composition yields more detailed and reliable information when compared with these oil and fat structure index tests and thus has improved the identity determination of fats and fixed oils. Because fatty acid composition can determine the percentages of each fatty acid group, structure indices such as iodine value and saponification value can be calculated or estimated based on the fatty acid composition profile (6–8). However, fatty acid composition is subject to considerable variation and presents challenges, the details of which are discussed in a later section.

Table I: Excipient monographs that have "oil" in the titles and that fall under the responsibility of the excipients expert committee.

Oil type	*USP 35–NF 30* through 2nd Supplement (2012)
Fixed oils	Almond Oil *NF*
	Castor Oil *USP* Hydrogenated Castor Oil *NF* Polyoxyl 35 Castor Oil (fixed oil derivative) *NF* Polyoxyl 40 Hydrogenated Oil (fixed oil derivative) *NF*
	Canola Oil *NF* Fully Hydrogenated Rapeseed Oil *NF* Superglycerinated Fully Hydrogenated Rapeseed Oil *NF*
	Coconut Oil *NF* Hydrogenated Coconut Oil *NF*
	Corn Oil *NF*
	Cottonseed Oil *NF* Hydrogenated Cottonseed Oil *NF*
	Olive Oil *NF*
	Palm Oil *NF* Hydrogenated Palm Oil *NF*
	Palm Kernel Oil *NF*
	Peanut Oil *NF*
	Safflower Oil *USP*
	Sesame Oil *NF*
	Soybean Oil *USP* Hydrogenated Soybean Oil *NF*
	Sunflower Oil *NF*
	Hydrogenated Vegetable Oil *NF*
Petrochemical oils	Mineral Oil *USP* Rectal Mineral Oil *USP*
	Light Mineral Oil *NF* Topical Light Mineral Oil *USP*
Essential oils	Anise Oil *NF*
	Peppermint Oil *NF*
	Rose Oil *NF*

Through the 2005 and 2006 revisions, the test for acid value was revised to include another titrant, to provide a calculation formula, and to add an additional test procedure allowing use of a different solvent mixture (9,10). The 2008 revision replaced all the descriptive texts used in the calculations under the test sections with the appropriate calculation formula (4). Additionally, three new test sections were proposed: omega-3 fatty acids determination and profile, trace metals, and sterol composition. These methods were introduced using a modern instrumental analysis approach. These additions enhanced the quality of General Chapter <401> by providing compendial users further analytical methods that help to better characterize and evaluate fats, fixed oils, and related substances and that ensure purity of fixed oils and absence of adulteration.

USP General Chapter Injections <1>. In 2006 stakeholders indicated that the test procedure for unsaponifiable matter described in general chapter <1> in *USP 28–NF 23* was unclear and created uncertainty with regard to reporting of results (11).

USP staff and EM2 EC concluded that the test criterion for unsaponifiable matter under Other Vehicles in Ingredients, Vehicles, and Added Substances in <1> was subjective and thus unsuitable for its intended purpose, but the EC acknowledged the importance of the test for unsaponifiable matter for injectable products because it measured impurities such as waxes, phospholipids, and proteinateous matter to which patients could be allergic.

In addition, the original cottonseed oil *NF* monograph did not provide quality specifications for use as an injection vehicle. As a result, the monograph required revision to reflect its use in an intramuscular injection product. The EC also considered additional specific tests and appropriate acceptance criteria for this specific grade of oil.

EM2 EC collaborated with the Parenteral Products—Industrial EC to revise the tests under Other Vehicles in Ingredients, Vehicles, and Added Substances in <1> by means of a proposed revision published in 2008 (12). A quantitative test procedure for unsaponifiable matter and a test for acid value replaced the previous test for unsaponifiable matter and the test for free fatty acids. Thus quantitative specifications for acid value and unsaponifiable matter were introduced. Three additional tests and acceptance criteria also were introduced into <1>: Peroxide Value, Water, and Limit of Copper, Iron, Lead, and Nickel. All three tests are crucial quality control measures for fixed oils used in parenteral drug formulations. Usually, specifications for peroxide value and water proposed under the Other Vehicles in <1> are more stringent than those implemented in the oils used for oral and topical products. The atomic absorption spectroscopy tests for limit of copper, iron, lead, and nickel, referred to as trace metals in General Chapter <401>, were preferable to the method of General Chapter Heavy Metals <231>. The quantitative trace metals test satisfied the accuracy requirements for much lower specification limits for parenteral products. If the oil had not been subjected to hydrogenation or if a nickel catalyst had not been used in processing, a note was included in the test for nickel stating that the test for nickel was not required, thus preventing unnecessary testing.

For cottonseed oil and other vegetable oils that have parenteral applications in drug formulations, the updated quality specifications in the Other Vehicles section in general chapter <1> were introduced and referenced in the fixed oil monographs.

Monograph labeling. A monograph's Labeling section may contain a labeling requirement to differentiate a specific grade or chemical composition of the excipient. If a highly purified fixed oil will be used in injectable dosage forms (i.e., qualified as a specific grade), this is indicated in the Labeling section. Additional quality specifications for the specific grade may be necessary and can be included in Other Requirements under the Additional Requirements section of the monograph.

Recommendations and criteria for modernization

Recommendations for fixed-oil monographs. Fixed-oil excipients are used in a large number of drug products and are essential to product safety and performance. Thus, the successful manufacture of a robust product requires the use of well-defined excipients and processes that together yield consistent product quality. Typically, excipients are manufactured and supplied to comply with compendial standards. *USP–NF* excipient monograph specifications are not designated to explicitly test for material functionality, except for co-processed excipients (13). A greater understanding of the chemical composition and the physical and chemical properties of excipients is necessary to set compendial specifications in *USP–NF* monographs.

Based on a literature review, comparative analysis of compendial specifications for fixed oil articles in *NF 23*, and studies of fixed oils using modern analytical technologies, USP staff and EM2 EC made the following recommendations to modernize fixed-oil monographs:

- Introduce identification tests that are specific for chemical composition. A fingerprint or chemical profile—not all components or constituents must be individually identified—should be considered. Where possible, test for a greater number of nonoverlapping attributes by introducing a greater number of relatively simpler tests. In best cases, these tests can be performed orthogonally. Introduce tests that are generic and can be applied to most (if not all) fixed oils.
- Introduce an oil chemical composition specification specific for relative compositional constituents such as fatty acids.
- Introduce tests that identify and quantify the ingredient itself (e.g., component triglycerides) rather than a surrogate.
- Introduce specifications to identify natural or deliberate transformation and stability.

These recommendations are discussed below.

Recommendations for test procedures. EXC EC proposes several criteria for test procedures for fixed-oil excipient monograph modernization:

- Universality of application
- Ease of adoption—uses existing equipment and methodology to the greatest extent possible
- Simplicity of procedure—a greater number of individual simpler tests is preferable to a smaller number of tests whose methodology is more complex and challenging
- Specificity—any test or combination of tests must be able to uniquely identify the fixed oil and exclude the presence of other oils
- Sufficient specificity to differentiate between an authentic fixed oil and an oil adulterated with the same oil of inferior quality
- Preferably identify as well as assay a fixed oil using one method.

Modernization strategy

USP staff and EM2 EC have developed an analytical test plan to fulfill the current regulatory requirements and keep abreast of current industry developments.

The analytical test plan for fixed oils is summarized in **Table II** and is presented in greater detail in the extended online version of this article (www.pharmtech.com/USPfixedoil). The tests recommended in **Table II** are critical control measures that ensure the identity, strength, quality, and purity of fixed oils. Further explanation and rationale to justify these recommendations are presented below.

Identification tests. *Spectroscopic identification and laboratory results.* In the USP 2005–2010 revision cycle, USP staff and EM2 EC identified excipient monographs that lacked an identification test and recommended introducing an infrared (IR) spectroscopy or similar spectroscopic identification test in preference to wet chemistry or colorimetric tests. Generally, spectroscopic procedures provide a good identification for highly purified single-molecular compounds. The USP Research and Development laboratory performed suitability studies for inclusion of an IR identification test in several fixed-oil monographs such as cottonseed oil, olive oil, peanut oil, safflower oil, and soybean oil. The results indicated that IR could not be used as a suitable identification test for these fixed oils because their IR spectra were

Table II: A strategic analytical test plan recommended in fixed-oil monographs.

Monograph Category	Tests
Identification	1. *Fatty Acid Composition* • Serves as a universal identification test (ID). However, because of broad ranges for individual fatty acids, it is not a stand-alone test. 2. *Melting Range or Temperature* • Used as an ID test if the melting range is small because it then accurately reflects the chemical composition and the crystalline forms of triglycerides present. However, some oils have a broad melting range so this test is not always appropriate as an ID. Melting range or temperature with a narrow and specific range can be used as an ID test. 3. *Thin-Layer Chromatography* • Serves as an orthogonal test to determine the identity of fixed oils and provides fingerprints of triglycerides in fixed oils 4. *Content of Triglycerides (or Triglyceride Composition)* • Serves as a stand-alone ID test
Assay (or composition)	1. *Content of Triglycerides (or Triglyceride Composition)* • Performed on an intact sample using HPLC or GC • Serves as an assay or composition test
Impurities	1. *Heavy Metals* • A necessary test for oils that are obtained from natural sources 2. *Alkaline Impurities* • Control residuals from alkali refining step 3. *Nickel* • A necessary test for hydrogenated oils; a possible residual catalyst 4. *Absence of Oil Substitute and/or Contaminant* • Example: Absence of Sesame Oil in the Revised Olive Oil NF monograph
Specific tests	1. *Acid Value* • Determines free fatty acids, an indicator for hydrolytic status of an oil product 2. *Peroxide Value* • Indicates primary oxidation products, an indicator of stability of an oil product 3. *Unsaponifiable Matter* • Measures unsaponifiable constituents, an average of 0.2%–2% unsaponifiable compounds 4. *Water* • Assesses moisture of oil product 5. *Sterol Composition* • Sterols are specific for each oil source, and a sterol composition analysis can reveal the identity of the components in a mixture.
Additional requirements	1. *Labeling* • Label to indicate any additives, if added. • Label to indicate a specific grade of oil, such as its application in injectable dosage forms. 2. *Other Requirements* • E.g., "For Soybean Oil intended for use in injectable dosage forms, which is specified in the Labeling, the requirements for *Acid Value, Peroxide Value, Unsaponifiable Matter,* and *Water* in the subsection *Other Vehicles* of the section *Ingredients* under *Injections* <1> must be met." • More examples are presented in the following: o Revised Soybean Oil *USP* [*PF* 34(4)] o Revised Cottonseed Oil *NF* [*PF* 34(5)] o Revised Corn Oil *NF* [*PF* 34(5)] o Revised Peanut Oil *NF* [*PF* 34(6)]

indistinguishable from each other, and IR was unable to uniquely identify fixed oils by visual comparison because of the similarities in their functional groups. Furthermore, ^{1}H nuclear magnetic resonance (NMR) spectroscopy was also considered; however, there were concerns related to cost, lack of NMR instruments in most quality-control laboratories in industry, and a lack of personnel training for the NMR procedure.

Fatty acid composition and melting range or temperature. Ideally, a robust specification should be independent of genetic modifications or seasonal or geographic variations that tend to change the composition of the substance over time and place. The fatty acid composition of a fixed oil, however, varies with natural, seasonal, and geographical changes. Thus, the specification commonly defines the widest possible compositional range that is acceptable from the viewpoints of safety, functionality, and effective extraction. Even so, the specification limits for the fatty acid composition should be narrow enough so that there is reasonable assurance that the substance is pure, not adulterated, not processed improperly or incompletely, and suitable for its intended use.

Thin-layer chromatography. In recent years, thin-layer chromatography (TLC), specifically high-performance TLC (HPTLC), increasingly has been used for lipid analysis (14,15). TLC/HPTLC is a specific, reproducible, cost-

effective, and routine quality-control analytical tool that provides a fingerprint identity for complex excipients such as fats, oils, and phospholipids. EXC EC has worked with the General Chapters Chemical Analysis EC and the USP laboratory to propose a new general chapter, Identification of Fixed Oils by Thin-Layer Chromatography <202> (16). USP plans to release 11 USP Fixed Oil Reference Standards in support of <202> (16). USP's Dietary Supplements department is planning to add three new fixed-oil dietary supplements to chapter <202> to support new monograph development.

Unique patterns of TLC bands from specific triglycerides can distinguish fixed oils of different botanical origins, so it can be used orthogonally in conjunction with fatty acid composition. The procedure is harmonized with *European Pharmacopoeia* general chapter 2.3.2. Identification of Fixed Oils by Thin-Layer Chromatography (17).

Assay. *Content of Triglycerides.* In recent decades, advances in chromatography and spectrometric methods (including mass spectrometry) have provided significant advancements in the understanding of complex excipient mixtures.

Some fixed oils from different plant sources yield characteristic patterns with distinct triglycerides that predominate (18). In many cases, the triglyceride pattern is more representative of the fixed oil identity than the fatty acid composition. This pattern can be determined with the help of HPLC or GC. A test for triglyceride composition based on an HPLC procedure using a refractive index detector was included in Sesame Oil *NF* in *USP 28–NF 23* (2005) (11). The test has an additional advantage because it can be performed on an intact sample, and it directly assesses the chemical composition of the oil and is recommended as an assay or composition test. If the test for triglyceride composition is introduced into fixed-oil monographs, it also can be used as a stand-alone identification test.

High-performance size-exclusion chromatography (HPSEC) is a useful analytical tool to identify and quantify triglycerides, diglycerides, and monoglycerides, as exemplified in Glyceryl Monostearate *NF*, Glyceryl Distearate *NF*, and Glyceryl Tristearate *NF* monographs in *USP 36–NF 31* (2013) (19). In the Lipid Injectable Emulsion USP monograph, HPSEC is used to determine soybean oil or other relevant oils used in the emulsion. Reports indicated that all triglycerides from soybean oil or other relevant oils are eluted as one peak under the test conditions, without separation. Although HPSEC cannot be used to differentiate fixed oils of different botanical origin, the amount of triglycerides in a fixed oil can be determined using the HPSEC procedure.

Specific tests. *Sterol composition.* The composition of fatty acids traditionally has been used as an indicator of purity, although the wide variation in the composition of edible oils from different geographical origins or different cultivars is a limiting factor in the interpretation of data with regard to adulteration. Sterols, which comprise a major portion of the unsaponifiable matter, are found in almost all fats and fixed oils, and they also are characteristic of the authentic fixed oil.

Sterols are highly specific for each oil source, and USP staff and EM2 EC recommended that the tests of fatty acid composition (from the saponifiable portion) and sterol composition (from unsaponifiable matter) be used orthogonally for certain fixed oils to determine their identity and quality. Because of characteristic sterol profiles and the high economic values of almond oil and olive oil, comprehensive sterol composition specifications have been implemented in both monographs. The sterol composition specifications in soybean oil *USP* and corn oil *NF* serve to exclude any other contaminating oils such as canola oil when these fixed oils are manufactured in the same facilities.

Test specifications. *Iodine value, saponification value, and some other physical methods.* Iodine value and saponification value tests are used to measure the degree of unsaturation and the relative proportions of fatty acids and glycerin in a sample, respectively. Introducing the fatty acid composition test into the monograph makes the iodine value and saponification value tests redundant because both values can be estimated from the fatty acid composition profile. Therefore, when the fatty acid composition test is part of the specifications of a fixed-oil monograph, the iodine value and

Table III: Continued monograph modernization for fixed oils.

Project Number	Fixed Oil	Activities
1	Fixed oils included in general chapter <202>	Addition of the TLC identification test as needed
2	Sterol Composition for Olive Oil *NF* and Soybean Oil *USP*	Replacement of the current TLC separation by a preparative HPLC separation during the sterol preparation step
3	Safflower Oil *USP*	Updating of the current Fatty Acid Composition test and introduction of identification test(s)
4	Sunflower Oil *NF*	Introduction of identification test(s)
5	Castor Oil USP	Introduction of identification test(s) and/or an assay (composition)
	Hydrogenated Castor Oil *NF*	
	Polyoxyl 35 Castor Oil *NF*	
	Polyoxyl 40 Hydrogenated Oil *NF*	
6	Sesame Oil *NF*	Monograph modification to accommodate a special grade that is used in injectable dosage forms

saponification value tests usually are not included or have been deleted from the monograph.

Other physical tests. Other tests such as specific gravity and refractive index that previously were included in several fixed oil monographs have been moved into the Description and Solubility section of *USP–NF* for the fixed oils. With the proposed modernization for the fixed oils, these physical tests provide added optional assurance of identification and purity of the fixed oils.

Conclusion

As shown in **Table III** and in the extended online version, excipient monograph modernization is a continuing endeavor that requires a consistent approach within a family of excipients. Such an approach is necessary to streamline analytical testing across multiple monographs as well as to keep the number of specific analytical tests to a minimum. This decreases the analytical burden on industry and allows methods to be referenced in monographs (e.g., from a general chapter).

USP continues to update *USP–NF* to provide standards for articles, including revised specifications based on advances in analytical and metrological science. USP ECs also rely on stakeholders' and sponsors' comments to keep monographs current. Emerging methodologies such as carbon number testing, C^{13}/C^{12} ratio testing, and chemometrics can be considered as they become commonly adopted by stakeholders.

Acknowledgments

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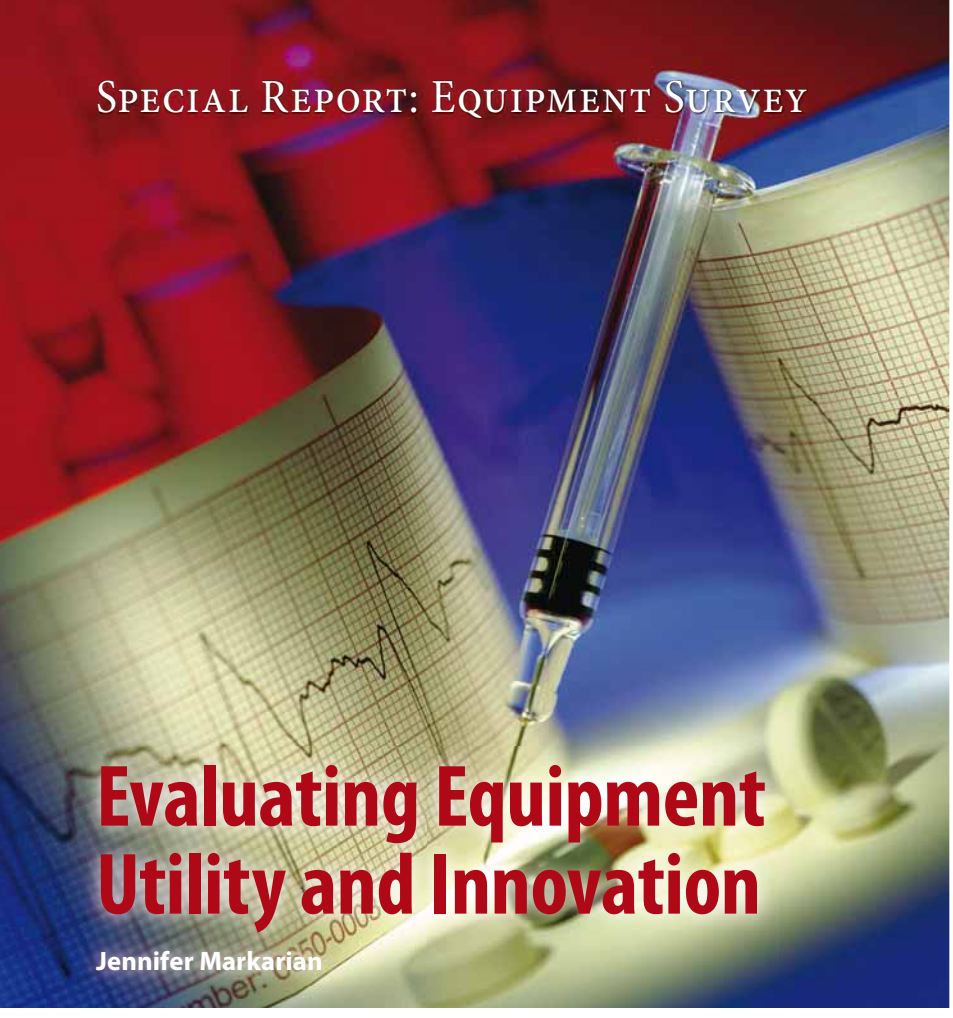
WEB For an expanded version of this article, visit PharmTech.com/USPfixedoil, or click on the QR code at right using your smart phone to go directly to the article.



Evaluating Equipment Utility and Innovation

Jennifer Markarian

Pharmaceutical Technology's survey of manufacturing equipment and trends shows satisfaction with utility and innovation in most solid dosage and parenteral drug-manufacturing equipment.

Pharmaceutical Technology's annual equipment and manufacturing survey gained the industry's perspectives on trends in finished drug-product manufacturing and equipment. Respondents in both solid dosage and parenteral drug manufacturing were generally satisfied with the utility of existing equipment and the pace of innovation in meeting manufacturing needs. Most employ quality by design (QbD) to some extent, but respondents identified a range of challenges in implementing QbD. Responses also indicated trends in high-potency/high-containment manufacturing, process analytical technology (PAT), and continuous manufacturing.

Solid-dosage equipment

The survey showed that existing solid-dosage equipment is generally meeting needs. Areas noted by more than 20% of respondents as needing significant improvement, however, included process control/automation, powder transfer/materials handling, and feeding/dispensing (see **Figure 1**). When asked if innovation is keeping pace with current and future needs, responses were similar, with the same three areas indicated as lacking solutions by 20% or more of respondents. Tablet compression stood out as a strongly innovative area, with 96% of respondents indicating that innovation is "excellent" or "good" for this equipment.

Parenteral equipment

Users of parenteral equipment, likewise, are generally satisfied with existing equipment, as shown in **Figure 2**. Process control/automation and vials/cartridges fill-finish equipment, however, were two areas noted by 20% or more of respondents as needing significant improvement. In all segments, nearly 80-90% of respondents said that the pace of innovation was "good" or "excellent".

High-containment/ high-potency manufacturing

Just over half of respondents that are involved in high-containment/high-potency manufacturing had seen an increase in activity in this area in the past year. Approximately one quarter of respondents said system setup/changeover was the most challenging factor in high-containment/high-potency manufacturing, while another quarter identified getting materials into or out of the contained system during production as the most challenging. Others identified air flow (10%), air-flow changes (10%), environmental issues (10%), containment (10%), personnel protection (7%) and ergonomics (3%) as the most challenging factor in high-containment/high-potency manufacturing.

QbD

Almost half of respondents indicated that their company applies QbD principles for both new and legacy products, and another 32% apply QbD to all or select new products (see **Figure 3**). Only 22% of respondents do not apply QbD at all. Approximately 72% identified better process understanding as a benefit of QbD. Participants were invited to choose all answers that applied, and they indicated other benefits of QbD

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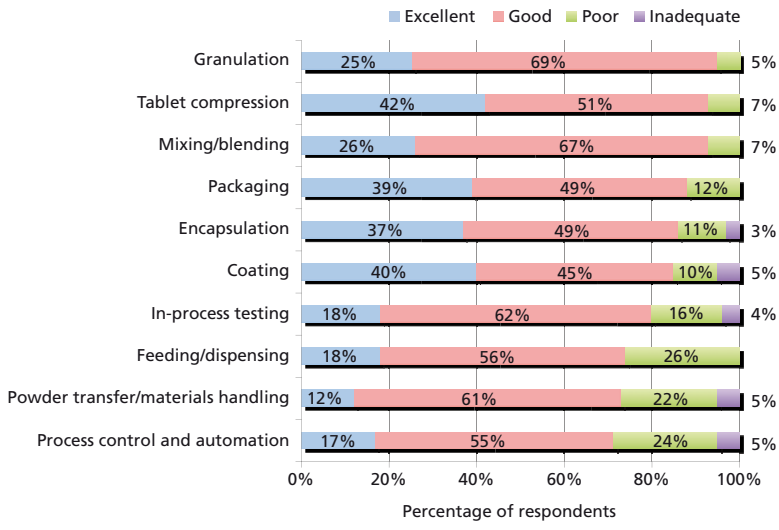
Figure 1: Utility of existing solid-dosage equipment in meeting needs (% of respondents).



Percentages may not equal 100% due to rounding

Figure 2: Utility of existing parenteral equipment in meeting needs (% of respondents).

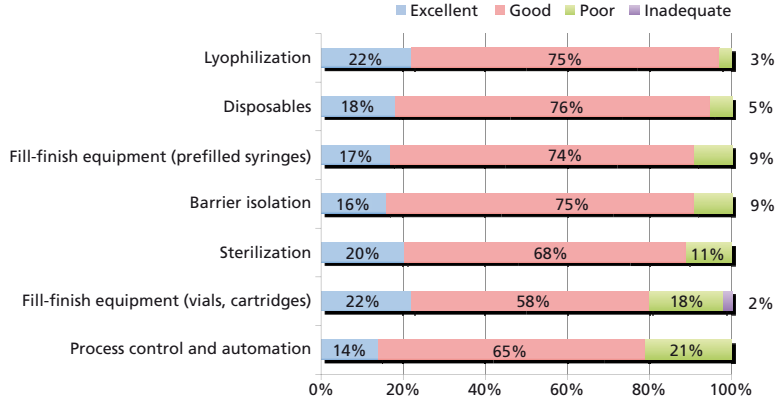
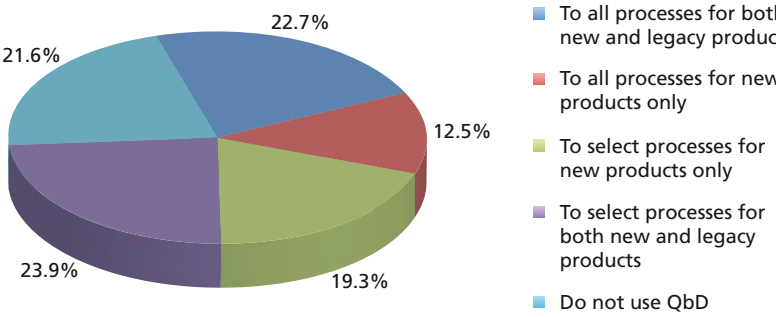


Figure 3: Application of quality-by-design (QbD) principles to manufacturing processes (% of respondents).



Respondents' profiles

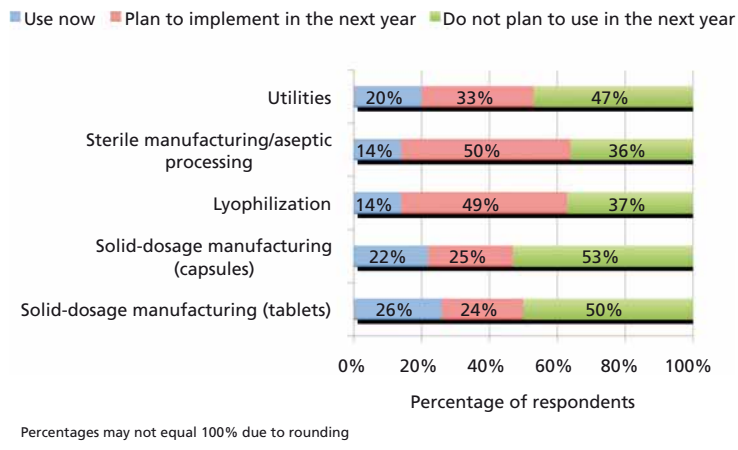
Pharmaceutical Technology's Equipment and Manufacturing Survey targeted individuals in production and engineering. The survey was conducted by email in February 2013 and had 193 respondents. Nearly 30% were from innovator pharmaceutical companies, 28% from generic-drug companies, 20% from contract manufacturers, and 10% from consumer healthcare companies making over-the-counter products. The remaining respondents included excipient and raw material suppliers (7%) and equipment or machinery vendors (5%). About half of the respondents were involved with solid-dosage manufacturing and the other half in parenteral drug manufacturing. The majority of respondents (79%) were from companies with under $1 billion in revenue. Nearly 7% were from companies with between $1 to $10 billion in revenue, almost 7% were from companies with $10 to $50 billion in revenue, and the remainder (8%) were from companies with over $50 billion in revenue.

as increased efficiency/reduced waste (48%), reduced costs (44%), shorter process times (35%), streamlining regulatory review (32%), and improved ease of making changes (29%). Only 6% of respondents felt that there are no challenges or barriers to implementing QbD. More than half noted lack of knowledge and training as a problem. Approximately 42% indicated clarity of regulatory guidance as a barrier. Only about one-third of repondents chose, respectively, lack of management buy in, availability of software, or availability of equipment as barriers to QbD implementation.

PAT

Over half of respondents indicate that they use PAT, which is an increase from last year's survey that found only 40% of respondents incorporating PAT (1). When asked to indicate the primary drivers for using PAT (multiple answers permitted), nearly half of respondents chose increased efficiency/reduced waste; others chose better process understanding (44%), reduced costs (33%), and shorter process times (31%). Almost 10%

Figure 4: Current and future use of process analytical technology (PAT) (% of respondents).



Percentages may not equal 100% due to rounding

indicated that their company mandates use of PAT, and nearly 6% said their customers request it. Sterile manufacturing/aseptic processing and lyophilization are areas of potentially strong growth for the use of PAT. As shown in **Figure 4**, 14% of respondents in these areas use PAT now, but an additional 50% plan to implement PAT in the coming year. Compared to the other categories, a higher percentage in solid-dosage manufacturing (22–26%) already use PAT, but a lower percentage (24–25%) plan to add PAT in the coming year.

Continuous manufacturing

Continuous manufacturing is still a new technology, but is being considered as an alternative to traditional batch processes for solid-dosage manufacturing. Respondents indicated (multiple answers permitted) multiple barriers to implementing continuous processes, including:

- lack of equipment (46%)
- insufficient expertise (42%)
- cost (36%)
- concern over regulatory acceptance (29%)
- insufficient PAT (23%)
- lack of appropriate documentation systems (15%).

Nearly all agreed, however, that technology will continue to evolve and use of continuous processing will increase.

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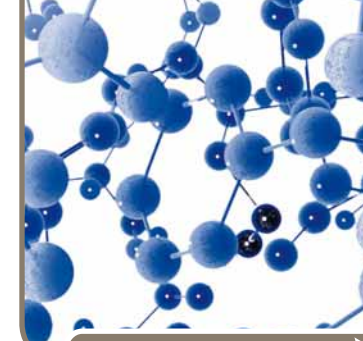

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Fine-Chemical Producers Make Targeted Investments

Patricia Van Arnum

Contract API manufacturers proceed with select investment in capacity and service additions.

Informex, the exhibition of custom and batch manufacturers, which was held in February in Anaheim, California, provided an opportunity to review recent activity in the fine-chemicals and contract API market. In examining developments from 2012 and 2013 to date, companies are proceeding with select investments to expand manufacturing capacity and enhance service capabilities. High-potency manufacturing continues to be an active area of investment among CMOs, and several CMOs also are expanding overall manufacturing capacity.

Company activity

Lonza, the bellwether of the contract API manufacturing sector, proceeded with several expansions in its small-molecule custom-manufacturing business in 2012. Earlier this year, Lonza reported that its custom manufacturing and bioscience sectors will be regrouped into one pharmaceutical market segments group.

In 2012, Lonza completed the first two build-out phases of its large-scale multipurpose cGMP API plant in Nansha, China, following FDA approval of several customer projects in late 2011. Also, the company successfully brought on line a small-scale manufacturing train and a GMP kilo-laboratory in Nansha. The company's large-scale antibody drug conjugates project in Visp, Switzerland was finalized on schedule, and the plant received FDA approval in the third quarter of 2012. A second expansion phase has started and will be finalized toward the end of the first half of 2014. Five additional high-potency API (HPAPI) laboratories in Visp, with capabilities for cytotoxic substances, are operational and utilized, and new investment in additional cytotoxic API manufacturing capacity in Visp was started up in 2012. Lonza also increased peptide-manufacturing capabilities at its site in Braine, Belgium.

High-potency manufacturing remains an active area of investment among CMOs.

Other companies are proceeding with investments and alliances to build HPAPI capabilities. In 2012, Carbogen Amcis and ADC Biotechnology formed a partnership to provide customers with development and manufacturing services for antibody drug conjugates. ADC Bio will provide access to proprietary solid-phase immobilization technologies for conjugation and long-term storage of antibody drug conjugates. Carbogen Amcis will focus on small- to large-scale GMP supply and on the formulation of antibody drug conjugates.

In October 2012, Fujifilm Diosynth Biotechnologies formed a strategic alliance with Piramal for antibody drug conjugate production, whereby the two companies will offer contract development and manufacture of antibody drug conjugates. Piramal offers antibody drug conjugate production at its site in Grangemouth, Scotland. In 2012, Fujifilm also expanded its cGMP manufacturing facilities at its sites in Research Triangle Park, North Carolina and Billingham, United Kingdom.

Novasep announced in 2012 a $3.9-million (EUR 3 million) investment to expand its HPAPI manufacturing capabilities at its facility in Le Mans, France. The plant expansion was scheduled to be fully operational by the beginning of 2013.

In addition to its HPAPI capacity expansion, Novasep is investing EUR 30 million ($39 million) to build a chromatography plant for the large-volume production of commercial APIs. The plant is being built on Novasep's existing site in Mourenx, France and is expected to be operational and validated in 2014 . The new plant will contain Varicol continuous chromatography systems with 1200-mm diameter columns operated at up to 70 bars.

Other developments

Several companies have announced overall manufacturing capacity additions. For example, Albemarle is expanding its manufacturing facility in Tyrone, Pennsylvania. The $30-million expansion builds on an earlier expansion that began operations in November 2012, which will result in an eventual 40% increase in reactor capacity for the company's custom-manufacturing business. The first increment of new capacity will be operational late in the first quarter of 2014.

In February 2013, PharmaZell added an additional manufacturing site to its European manufacturing network. The company acquired a manufacturing

site in Liestal, Switzerland previously operated by AbbVie (formerly Abbott). Abbott's pharmaceutical business was spun off in a separate company, AbbVie, in January 2013. The Liestal site consists of multipurpose manufacturing equipment with 150 m^3 of reactor volume with drying and milling capacity, packaging cleanrooms, a pilot plant, quality-control laboratories, and warehouses for manufacturing small-molecule, large-volume APIs.

In 2012, Almac expanded its API manufacturing facility at its European headquarters in Craigavon, United Kingdom, with a scheduled completion for the end of 2012. The upgrade included installation of two 1000-L reactors and a pressure-filter dryer, which allows production of GMP APIs up to 150-kg batches.

In September 2012, Cambridge Major Laboratories (CML) reported that it is expanding its large-scale API manufacturing facility in Germantown, Wisconsin. The expansion comes three years after commissioning the new site. The expansion includes additional reactor capacity and isolation equipment as well as additional investments in engineering controls. Also, in 2012, Cedarburg Hauser Pharmaceuticals expanded its capacity at its Wisconsin-based API manufacturing plant and made additional upgrades for improving safety and GMP systems.

Other companies are making targeted investment in select manufacturing activities. In 2012, Dr. Reddy's Custom Pharmaceutical Services expanded its activated mPEG manufacturing capabilities at is facility in Mirfield, United Kingdom. SAFC, part of Sigma-Aldrich, is expanding its operations in Scotland by investing in the development of a new powder-manufacturing facility at its Irvine site. SAFC's new facility in Irvine is its second powder manufacturing facility, which will support SAFC's risk-management program, which provides an internal back-up supplier for its customers. The new facility will be used to serve customers across Europe.

Almac and DSM Pharmaceutical Products recently reported the successful transfer of enzymes for enzyme screening, process development and scale-up as part of the companies' agreement in biocatalysis, which was announced in October 2012. The agreement grants both companies access to their enzyme platform technologies and services for the manufacturing of APIs. The collaboration also enables Almac to offer its customers a preferred partner for large-scale production.

In February 2013, DSM Pharmaceutical Products signed an agreement with Chemtrix, a supplier of flow-chemistry equipment and services, for providing equipment, development and manufacturing services to the pharmaceutical industry. Chemtrix specializes in ready-to-use laboratory and kilo-scale microreactors as well as reactor and process design for industrial reactors. DSM provides drug-synthesis

route development, scale-up, and implementation of continuous-flow processes for manufacturing. DSM has FDA approval for using microreactors for making a pharmaceutical product at commercial scale under cGMP at its facility in Linz, Austria, where its dedicated commercial-scale installation is located. The DSM–Chemtrix collaboration will initially offer an industrial flow process-development package for customized scalable flow-chemistry solutions. The package covers all phases of process design, scanning chemistries, chemistry development, route scouting, equipment design, and scale-up for fully continuous or integrated processes.

Albemarle is investing $30 million in its custom-manufacturing facility.

Ajinomoto plans to invest approximately JPY 1.3 billion ($13.9 million) to double production capacity for amino acids for use in pharmaceuticals and foods at its subsidiary Shanghai Ajinomoto Amino Acid in Shanghai. The expansion is scheduled to come on line in October 2013. Ajinomoto estimates the current global market for amino acids for pharmaceuticals and foods at 30,000 tons, and with growth in emerging markets, expects demand to rise to 45,000 tons by 2020.

Several fine-chemical producers and contract API producers also recently announced activity in support of finished product manufacturing. For example, earlier this year, Ajinomoto agreed to acquire Althea Technologies, a San Diego-based contract provider of fill–finish services. Aesica and the CDMO EmulTech are partnering on the commercial development of ET4ME, an emulsion technology for product formulation. ET4ME is a microencapsulation technology that uses a microfluidic process to create a measurable microparticulate suspension. The technology can be used for small molecules and biologics.

Cambrex agreed to contract manufacture Dow Chemical's hydroxypropyl methylcellulose acetate succinate, an excipient provided by Dow as part of a solubilization partnership that Dow and Bend Research formed in 2012 under which Dow is commercially supplying solubility-enabling excipients. Cambrex has begun construction of the new facility at Cambrex's site in Karlskoga Sweden with commercial product availability set for year end 2013. In another development, ScinoPharm and Foresee Pharmaceuticals agreed to form a joint venture to develop a series of peptide injectable drugs, with the first being a leuprolide injectable drug product, by which leuprolide will be formulated in a proprietary controlled-release drug delivery system originally developed by Foresee and transferred to the joint venture. ScinoPharm is investing $3.6 million for a minority ownership in the new company. **PT**

Optimizing Quality by Design in Bulk Powders & Solid Dosage

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EVENT OVERVIEW:

The changing paradigm resulting from FDA's Quality by Design (QbD) initiative and ICH guidelines requires increased process understanding of the drug substance and drug product throughout development and manufacturing. A lack of information can result in delays in regulatory approval and higher costs. Applying QbD leads to greater process understanding to facilitate regulatory approval, including post-approval changes.

This 60-minute webinar will provide practical insight and case-study analysis from leading industry experts on how to apply QbD by learning how to define critical quality attributes, implement risk assessment, optimize process development, develop a design space, perform criticality analysis, and execute a control strategy.

Presenters

Conrad Winters
Director, Drug Product Development
Hovione

Filipe Neves, PhD
R&D Drug Product Development (DPD) Group
Hovione FarmaCiencia SA

Moderator:

Patricia Van Arnum
Executive Editor
Pharmaceutical Technology

Key Learning Objectives:

- Understand the main stages and associated goals of a QbD methodology;
- Learn the recommended tools/ procedures for each stage of a QbD methodology;
- Consolidate the knowledge through two case-studies involving bulk powders and solid dosage forms.

Who Should Attend:

- Chief scientific officer
- Directors, group leaders, and managers of quality, QA/QC, and compliance
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Strategic Partnering for Manufacturing

Jim Miller

Eisai and Biogen Idec pursue an innovative approach to capacity management.

Managing manufacturing network capacity has been a major challenge for bio/pharmaceutical companies for more than 10 years. As industry economics change and products lose patent protection, companies have been faced with the problem of reducing or eliminating the costs of underutilized facilities. Further, because of their heightened attention to risk and the need to conserve capital for licensing deals and acquisitions, bio/pharmaceutical companies want to avoid making manufacturing investments whenever possible.

Typically, companies have pursued two paths for dealing with their capacity utilization problem: closing or divesting unnecessary facilities, or going to into the CMO business as a way of absorbing the capacity.

Facility closures are the most direct approach and are relatively straightforward to accomplish in North America, but they are more difficult in Europe because of social regulations and negative publicity. In both Europe and North America, divesting the facility to another bio/pharmaceutical company or to a contract manufacturer has been a viable alternative. This approach has its drawbacks: the sale process can be long and drawn out, and in a few extreme cases, the bio/pharmaceutical company has been forced to take back the facility when the CMO option has proven not to be viable to safeguard product supply.

Where an underutilized facility still has strategic value, the bio/pharmaceutical company may seek to sell the excess capacity in the contract manufacturing market. This typically has marginal benefit, however, as the bio/pharmaceutical company seldom allocates the necessary resources to the business and is so selective about the projects it will take that it signs very few deals.

Eisai and Biogen Idec have established a strategic partnership that they believe can serve as a model for manufacturing capacity management.

Strategic alternative

In recent months, two bio/pharmaceutical companies have announced a new and more innovative approach that may be a much better alternative to closure, divestiture, or contract manufacturing. Eisai and Biogen Idec have established a strategic partnership that they believe can serve as a model for manufacturing capacity management for the bio/pharmaceutical industry.

Under the terms of the agreement, which became operational on Feb. 1, 2013, Biogen Idec is leasing part of an Eisai solid-dose manufacturing facility in Research Triangle Park, N.C. (RTP), and is manufacturing oral solid-dose products for itself and for Eisai in the leased facility. In a parallel arrangement, Eisai will fill and finish Biogen Idec biologics products at its injectable manufacturing facility in RTP, as well as package the oral solid-dose products.

The 10-year lease agreement gives Biogen Idec the option to purchase the Eisai solid-dose facility. Approximately 50 Eisai personnel have moved to Biogen Idec to support the solid-dose manufacturing.

The partnership grew out of the confluence of challenges that the two companies were facing. Eisai had to address the utilization problem at its solid-dose facility as its Alzheimer's treatment Aricept approached loss of exclusivity, said Lou Arp, general manager of Eisai's RTP manufacturing site and president of global oncology manufacturing. For its part, Biogen Idec needed to bring small molecule capability in-house and add more capability to its supply chain to reduce risk, according to Machelle Sanders, vice-president of manufacturing and general manager of its RTP manufacturing site. Solid-dose products are new territory for Biogen Idec, which has traditionally focused on biologics.

The two companies were familiar with each other's capabilities and culture well before their discussions began. For one, their two facilities are located in close

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proximity to each other in RTP. In addition, both have been involved in a manufacturing group within The North Carolina Biosciences Organization and have benchmarked each other's best practices as part of that group.

Both Sanders and Arp say that their partnership is truly strategic and different from a traditional CMO deal. They describe it as a "reciprocal and co-dependent relationship," in which issues that arise will have to be handled consistently for both parties. So, for instance, the way in which Biogen Idec resolves a problem in the manufacture of an oral solid-dose product for Eisai will be reflected in (or reflective of) how Eisai handles a similar problem in the manufacture of injectable products for Biogen Idec. The sometimes-adversarial relationship that can arise in a traditional CMO-client relationship can't be tolerated in their partnership, they contend.

As one might expect, governance will be a key to success in the partnership. The two companies have established a joint steering committee consisting of three representatives and director-level leadership from each. Manufacturing, engineering, and quality professionals are included on the committee.

Both Sanders and Arp maintain that the compatibility of their corporate cultures will be the central factor for the partnership's success. "Finding the right partner with the right values" was crucial in establishing the relationship, and the fact that they are both mid-size companies able to be flexible and nimble is also important.

Mixed sourcing strategy

For both Biogen Idec and Eisai, the new manufacturing partnership is part of a sourcing strategy in which both internal capacity and CMO relationships are key components. Biogen Idec has traditionally outsourced its fill-and-finish requirements while maintaining its own large molecule API manufacturing facilities. While it will manufacture its own products at the leased Eisai facility, it has also outsourced the manufacture of a new solid-dose product in its pipeline.

Eisai plans to continue to invest in its injectables capabilities to support its own pipeline, and sees the additional volume from Biogen Idec as helping to justify the additional investment. However, Eisai will use CMOs where appropriate: it recently announced a three-year master supply agreement with DSM Pharmaceutical Products for manufacture of eribulin mesylate (Halaven) at DSM's Greenville, N.C., injectables manufacturing facility.

Whether the partnership between Biogen Idec and Eisai is just a one-off event or becomes a model for the industry remains to be seen. It may be that unique factors like geographic proximity, interpersonal dynamics, and complementary needs facilitated an innovative approach that may be hard to duplicate. Or it may be that having seen this example of a new partnership approach, other bio/pharmaceutical companies start looking for innovative alternatives to addressing their manufacturing requirements. **PT**

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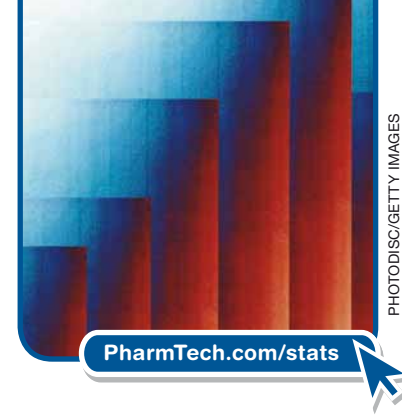

PHOTODISC/GETTY IMAGES

Rounding Results for Comparison with Specification

Chris Burgess

How to obtain unbiased rounding

Rounding a result to the required number of decimal places is easy, isn't it? After all, we were all taught at college or university that only two rules are needed.

Rule 1: If the digit after the figure to be rounded is less than 5, then don't change the rounded figure (i.e., round down).

Rule 2: If the digit after the figure to be rounded is 5 or more, then increase figure to be rounded by 1 (i.e., round up).

Simple really, isn't it? After all, the *United States Pharmacopeia* (*USP*) requires the use of just this method:

When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1 (1).

Of course, rounding only takes place after the final calculation has been performed. The *USP* General Notices make this requirement clear:

Numbers should not be rounded until the final calculations for the reportable value have been completed. Intermediate calculations (e.g., slope for linearity) may be rounded for reporting purposes, but the original (not rounded) value should be used for any additional required calculations (1).

Figure 1: Decision tree for an unbiased rounding process.

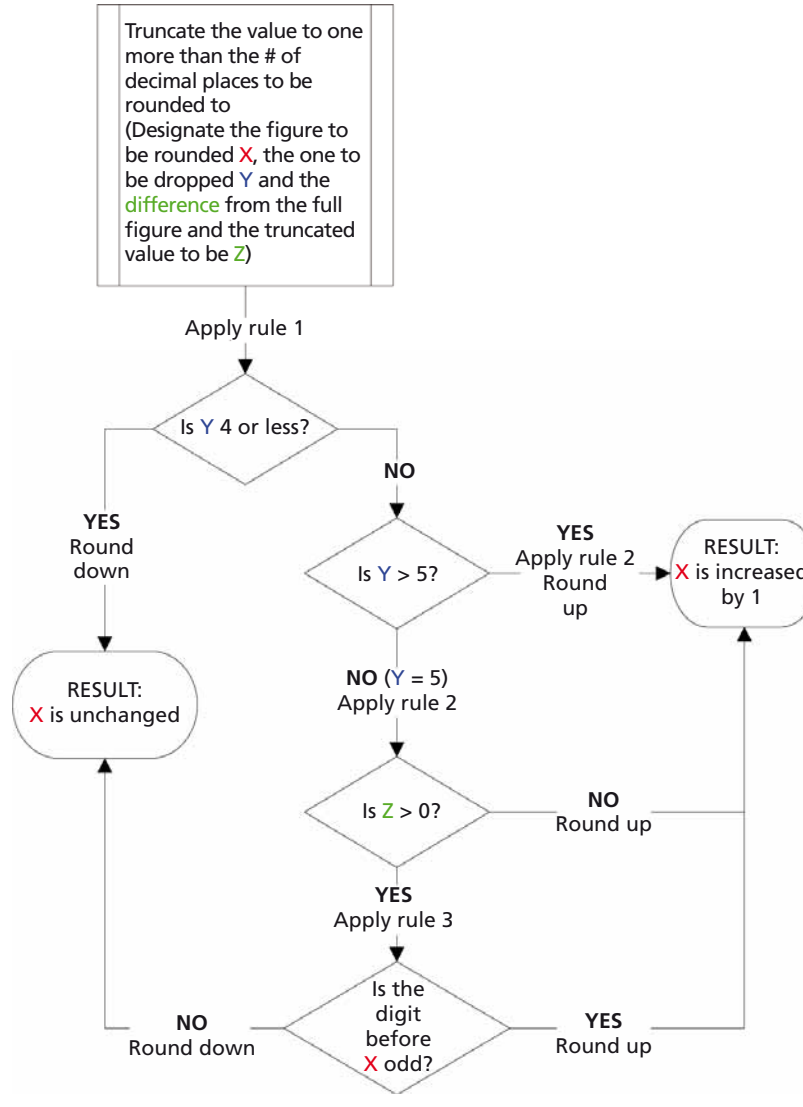

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Table I: Results from Excel 2010 with four examples.

Example	Correct value	ROUND	ROUND DOWN	ROUND UP
3.141593	3.14	3.14	3.14	3.15
2.718282	2.72	2.72	2.71	2.72
0.005051	0.01	0.01	0.00	0.01
0.005000	0.00	0.01	0.00	0.01

Table II: Results of the unbiased rounding formula using Excel.

Example	Correct value	# of decimals	Truncate	X	Y	Z	Rounding formula value
3.141592654	3.14	2	3.14150000000000	4	1	5.9265E-04	3.14
2.718281828	2.72	2	2.71820000000000	1	8	2.8183E-04	2.72
0.005051	0.01	2	0.00505000000000	0	5	5.1000E-05	0.01
0.005000	0.00	2	0.00500000000000	0	5	0.0000E+00	0.00

The problem is that simplicity is not always correct all the time. From a statistical point of view, applying rule 2 will bias the data over time because one will always round up particularly if 5 is frequently the figure to be rounded. 4 and below and 6 and above are balanced in rounding but what about 5? It has been known for more than 60 years that applying only rules 1 and 2 will cause biased data. What is even more interesting is that the third rule was well known at that time, at least to statisticians. Sadly, this rule is rarely if ever mentioned in modern text books and guidelines.

The need for simplicity does not take precedence over scientific correctness.

The purpose of this column is to resurrect this "forgotten" rule because the need for simplicity does not take precedence over scientific correctness. In any event, rule 3 is not hard to understand and is merely buried in older textbooks and standards.

Three rules for rounding

The best explanation of unbiased rounding is in a 1947 textbook written by the statistical research group of Columbia University (2). The senior editor, Churchill Eisenhart from the (then) National Bureau of Standards, was one of the most influential statisticians of his era.

Here are the three rules:

Rule 1: If the last digit to be dropped is less than 5, the last digit retained shall be left unchanged.

Rule 2: If the last digit to be dropped is greater than 5, or is 5 followed by digits greater than 0, the last digit retained shall be increased by 1.

Rule 3: If the last digit to be dropped is 5 alone or a 5 followed by 0 only, the last digit retained shall be rounded to the nearest even number.

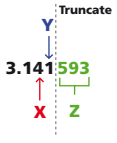
It is usually easier to see how such a rule works if you draw it in a decision tree as shown in **Figure 1**. In this figure, we designate the digit or figure to be rounded by X, the digit

or figure to be dropped by Y, and the difference between the truncated value and the full figure value by Z. Based upon the values of X, Y, and Z, we can arrive at the correct unbiased rounding decision.

Examples

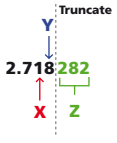
We can now test our unbiased rounding process with four examples.

1. Round π with 7 significant figures to 2 decimal places.



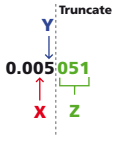
Rule 1 gives the answer 'Yes,' so round down to 3.14.

2. Round energy (E) with 7 significant figures to 2 decimal places.



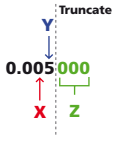
Rule 1 gives the answer 'No' and the rule 2 answer is 'Yes,' so round up to 2.72.

3. Round 0.005051 to 2 decimal places.



Rules 1 and 2 both give the answer 'No,' therefore, rule 3 is invoked. As Z > 0, rule 3 answer is 'No,' so round up to 0.01.

4. Round 0.005000 to 2 decimal places.



Rules 1 and 2 both give the answer 'No,' therefore, rule 3 is invoked. As Z=0, rule 3 answer is 'Yes' and the digit before X is even, therefore, round down to 0.00.

The last example may give rise to surprise because by the simple rules it would be deemed incorrect. However, it would be unlikely to find such an example in analysis unless the method is only capable of giving rise to 5 or 0 for Y.

Rounding using Microsoft Excel

Many laboratories use Microsoft Excel for calculations, so it is interesting to see how it performs with the four examples. Excel has three rounding functions—round, round down, and round up. In each function, it is necessary to specify the number to be rounded and the number of decimal places required. The results from Excel 2010 for the examples to 2 decimal places are shown in **Table I**. The incorrect rounded values are highlighted in yellow.

The round function works well with the exception of example 4. However, Excel can be easily programmed to perform a unbiased rounding decision tree automatically. Suppose the values to be rounded are put starting in cell C9 and the number of decimal places to be rounded to in cell E9.

Excel's 'trunc' function can be used to extract the values of X, Y and Z; using the formulae:

For X = TRUNC($C9,$E9)*10^$E9-TRUNC($C9,$E9-1)*10^$E9

For Y = TRUNC($C9,$E9+1)*10^($E9+1)-TRUNC($C9,$E9)*10^($E9+1)

For Z = $C9-TRUNC($C9,$E9+1).

These values of X, Y and Z are stored in the relevant rows (9 to 12) of columns G, H, and I. The rounding calculation formula (a nested "if" formula) is now placed in cell J9 for the first example and copied down for rows 10, 11, and 12 for the others:

Excel can be easily programmed to perform a unbiased rounding decision tree automatically.

=IF($H9<=4,ROUNDDOWN($C9,$E9),IF($H9>=5,IF(AND($H9>=5,$I9>0),ROUNDUP($C9,$E9),ROUNDDOWN($C9,$E9))))

The Excel results of the unbiased rounding formula are shown in **Table II** and agree with the manual evaluation for the four examples.

The mysteries of rounding are exposed here and strict unbiased rounding can be applied.

References

1. *USP* 35, General Notices 7.20, "Rounding Rules" (US Pharmacopeial Convention, Rockville, MD, 2012).
2. C. Eisenhart, M.W. Hastay, W.A. Wallis, *Selected Techniques of Statistical Analysis*, (McGraw-Hill, New York, 1947). **PT**

Quality by Design Approach for Stability Testing

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Key Learning Objectives:

- Learn how to implement quality-by-design (QbD) in your stability-testing programs.
- See how stability studies can facilitate a QbD approach to drug release and ensure product stability.
- Gain best practices for testing for water activity and moisture, including how to mitigate API hydrolysis, crystallization's effect on dissolution rates, caking or clumping of powders, and moisture migration.

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Brabender Pharma USA specializes in the manufacturing of GMP-compliant twin-screw extruders for hot melt extrusion (HME) applications. The effort has been to concentrate on top-quality equipment to produce small batch sizes up to pilot-scale processes. Brabender Pharma USA provides extrusion solutions. **Brabender Pharma USA,** *South Hackensack, NJ • www.brabender-pharma.com • tel. 201.343.8785*

OUTSOURCING & CONSULTING SERVICES

Contract development and manufacturing services

Halo Pharmaceutical is a contract development and manufacturing organization that provides scientific, regulatory and development expertise and a wide spectrum of manufacturing services to help customers bring their products to market quickly, effectively and on budget. **Halo Pharmaceutical,** *Whippany, NJ • www.halopharma.com • tel. 973.428.4087*

Manufacturing and raw-material testing

Incorporating its Avrio parenteral manufacturing facility into the Irvine brand in January was the first step in Irvine's three-prong initiative for aggressive yet stable growth: more highly trained technical personnel, new instrumentation and increased capacity for formulation, biopharmaceuticals and raw-material testing. **Irvine Pharmaceutical Services,** *Irvine, CA • www.irvinepharma.com • tel. 877.445.6554*

Contract development and manufacturing services

JHP is a fully integrated specialty pharmaceutical company that acquires, develops, manufactures, and sells sterile injectable and ophthalmic/otic products. JHP's cGMP-compliant manufacturing facility sits on over 80 acres and includes a 171,000-ft^2 production building and warehouse. JHP employs more than 370 staff serving hospitals, physicians and contract manufacturing customers. **JHP Pharmaceuticals,** *Parsippany, NJ • www.jhppharma.com • tel. 877.906.7556*

OUTSOURCING & CONSULTING SERVICES

Drug-development services

Vetter's development service provides support for drug-development projects from inception to market launch. The services include clinical manufacturing at facilities in Chicago and Europe with scale-up and transfer to Vetter's large-scale manufacturing facilities. The services provide primary- and secondary-packaging development, process development, clinical manufacturing, pharmaceutical analysis, and regulatory affairs services. **Vetter Pharma International USA,** *Skokie, IL • www.vetter-pharma.com • tel. 847.581.6888*

Contract services

Metrics is a CDMO that provides services in solid-dose development, including pharmaceutical formulation development; first-time-in-man formulations; clinical material manufacturing for Phases I, II, and III; and analytical method development and validation services leading to commercial scale manufacturing. Metrics' technical capabilities include expertise in highly potent, cytotoxic, insoluble, and unstable compounds and Schedule II–V controlled substances. **Metrics,** *Greenville, NC • www.metricsinc.com • tel. 252.752.3800*

Outsourced services

Pfizer CentreSource provides solutions for sterile manufacturing, high-containment manufacturing, and oral and solid dosage forms. Its capabilities draw upon Pfizer's global network of facilities, technologies, and expertise to fulfill a broad range of sourcing and outsourcing requirements, regardless of dosage form, batch size, or the complexity of the process. **Pfizer CentreSource (PCS),** *Kalamazoo, MI • www.pfizercentresource.com • tel. 269.833.5844*

OUTSOURCING & CONSULTING SERVICES

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Contract-manufacturing services

Hospira's One 2 One business specializes in contract manufacturing of injectable products packaged in vials, prefilled syringes, cartridges, flexible containers, and ampoules. Additional offerings include product development and fill–finish of clinical trial materials, registration, and commercial batches. The company's range of capabilities spans biologics, potent drugs, vaccines, cytotoxics, controlled substances, and lyophilization. **Hospira One 2 One,** *Lake Forest, IL • www.one2onecmo.com • tel. 224.212.2267*

3M

Drug-delivery solutions

3M Drug Delivery Systems provides manufacturing services for pharmaceutical and biotechnology companies. The company will exhibit at INTERPHEX New York (Apr. 23–25, 2013) at booth #2143 to display its inhalation and transdermal drug-delivery technologies. **3M Drug Delivery Systems,** *St. Paul, MN • www.3M.com/DDS • tel. 800.643.8086*

Bioanalytical analysis

MPI's senior scientists develop and validate assays to support development from preclinical to Phase I–IV clinical research. The company's specialized capabilities include mass spectrometry of small molecules, proteins, peptides, thermal analysis, immunochemistry, and residue analysis. **MPI Research,** *Mattawan, MI • www.mpiresearch.com • tel. 269.668.3336*

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Product-development guidance

The Dow dermatology and ophthalmic drug-development teams provide clear strategies to guide drugs, biologics, or medical devices through the regulatory approval process. Dow's staff has decades of experience successfully managing nonclinical, clinical, and regulatory programs for several pharmaceutical, medical device, and biotechnology companies. **Dow Pharmaceutical Sciences,** *Petaluma, CA • www.dowpharmsci.com • tel. 707.793.2600*

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Dosage-form services

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CHEMIC

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Chemic Laboratories is a full service cGMP/GLP contract analytical-chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including: extractables and leachables analysis, method development and validation, quality control analysis, release testing, raw-materials analysis, compendial testing, bioanalysis, organic synthesis and formulation development, and ICH stability testing. **Chemic Laboratories,** *Canton, MA • www.chemiclabs.com • tel. 781.821.5600*

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Contract services

Mikart has provided contract development, manufacturing, and packaging services to the pharmaceutical industry since 1975. The company's capabilities include formulation development; analytical services; solid- and liquid-dose manufacturing; packaging in bottles, blisters, and multilaminate pouches; project management; and regulatory services. **Mikart,** *Atlanta, GA • www.mikart.com • tel. 888.4 MIKART*

CLEANROOM EQUIPMENT & SUPPLIES

Cleanroom garments

Precision Fabrics Group's Integrity Barrier Fabrics are constructed with Integrity triple-barrier protection and are designed to increase comfort levels during use. The garment is intended for cleanroom operations, and is also designed to enhance product quality. **Precision Fabrics Group,** *Greensboro, NC • www.precisionfabrics.com • tel. 888.733.5759*

Mop frame

Perfex's swivel mop frame is constructed of high-grade stainless steel, and uniformly applies cleaning and sanitizing agents to floors, walls and ceilings, baseboards, and confined areas such as corners or stairs. The low-profiled mop frame allows for easy and efficient cleaning under tables or other hard to reach surfaces. The TruCLEAN Mop Frame delivers continual surface contact at any angle and is accurately balanced for non-flipping. **Perfex,** *Poland, NY • www.perfexonline.com • tel. 800.848.8483*

CLEANROOM EQUIPMENT & SUPPLIES

Laboratory cleaning system

The Core2Clean Plus System incorporates spray, mop, and fog capabilities into one unit. The system provides a clean solution to the surface each time, thus eliminating cross contamination from dirtied solutions. The system is designed to simplify moving from one controlled area to another by eliminating the requirement to make a new solution. **Veltek,** *Malvern, PA • www.sterile.com • tel. 610.644.8335*

Compounding cleanrooms

Terra's compounding cleanrooms are suitable for compounding sterile injectables and other preparations in accordance with *US Pharmacopeia* <797> standards. An ISO 5 (Class 100) primary processing area with three HEPA filter–fan units provides a total of 1950 cfm (3315 m^3/h) of 99.99% particle-free air (measured at 0.3 µm diameter). **Terra Universal,** *Fullerton, CA • www.terrauniversal.com • tel. 714.578.6190*

PACKAGING EQUIPMENT & SUPPLIES

Packaging solution

The Next-Bottle 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

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*

Blow–fill–seal machine

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

LABORATORY EQUIPMENT & SUPPLIES

Process analytical sensors

Hamilton Company manufactures application-oriented pH, ORP, dissolved oxygen, and conductivity sensors distinguished by their high quality, long life, and competitive price. Our intelligent VisiFerm optical dissolved oxygen probe offers technology that sets new standards in DO measurement. Hamilton Arc revolutionizes process analytics by replacing the traditional transmitter with a microprocessor within the sensor. **Hamilton Company,** *Reno, NV • www.hamiltoncompany.com/sensors • tel. 800.648.5950*

LABORATORY EQUIPMENT & SUPPLIES

Chromatography analytical system

Waters' ACQUITY UPC^2 System is designed for convergence chromatography applications. This powerful chromatographic technique uses compressed CO_2 as the primary mobile phase to leverage the chromatographic principles and selectivity of normal phase chromatography while providing the ease-of-use of reversed-phase liquid chromatography. **Waters,** *Milford, MA • www.waters.com • tel. 508.478.2000*

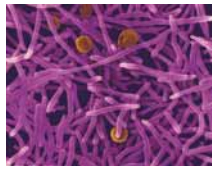
On-line TOC analysis

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

Laboratory blenders

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

LABORATORY EQUIPMENT & SUPPLIES



Quality control testing services

Charles River has combined its Endosafe rapid endotoxin-testing systems with Accugenix contract microbial identification services to offer a complete QC testing solution. Endosafe cartridge technology is designed to improve operational efficiencies by enhancing ease-of-use and accelerating testing times. Microbial identification is conducted in an FDA-registered lab using the Accugenix DNA sequence library. **Charles River Laboratories,** *Wilmington, MA • www.criver.com • tel. 781.222.6000*

Anion exchange column

Hamilton's RCX-30 Anion Exchange Column is designed to handle higher flow rates while maintaining a lower back pressure, delivering a faster analysis than similar columns offered by other manufacturers. The RCX-30 is also designed to expedite the determination of glucose levels in nutrition solutions. **Hamilton Bonaduz,** *Bonaduz, Switzerland • www.hamilton.ch • tel. +41 (0)81 660 67 41*

Die condition monitor

I Holland's Holland Die Condition Monitor (HDCM) is designed to monitor the condition of die bores, for any die type including multi-tips. When used at regular intervals, it ensures that optimum life is achieved from dies and helps to prevent the production of damaged tablets. **I Holland,** *Nottingham, United Kingdom • www.iholland.co.uk • tel. +44 (0) 115 972 6153*

LABORATORY EQUIPMENT & SUPPLIES

Spectroscopy and imaging systems

Advantest offers bench top spectroscopy and imaging systems for the pharmaceutical R&D market. The configurable and compact TAS7500 THz systems use proprietary terahertz wave technology to acquire characteristic spectra based on crystalline structure and 3-D images yielding tablet coating thickness and uniformity, and the nondestructive detection of cracks and voids in the tablet core. **Advantest,** *Princeton, NJ • www.advantest.com • tel. 609.799.0797*

Laboratory and processes catalog

Cole-Parmer's 2013–14 SOURCEbook features product solutions for laboratory and processes in a 2640-page catalog. Items include electrochemistry, fluid handling, research, biotechnology, and more. The catalog contains technical data for your reference and contact information for expert technical assistance. Call 800.323.4340 or go to ColeParmer.com/19794 to request a free copy. **Cole-Parmer,** *Vernon Hills, IL • www.coleparmer.com • tel. 800.323.4340*

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EtQ's GMP Regulatory Compliance Software is an integrated quality management and FDA compliance management software system that has been designed to maintain compliance with various regulatory requirements and adapt to business processes. EtQ's modules are tightly integrated to deliver a best-in-class solution for the Life Science industry and include eMDR, Complaint Handling, CAPA, eValidator, Change Management, and more. **EtQ,** *Farmingdale, NY • www.etq.com • tel. 800.354.4476*

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S2K for Pharma is a completely integrated ERP software solution that helps pharmaceutical companies meet industry-specific regulations and institutional requirements, while improving efficiencies and increasing customer satisfaction. The software is designed to assist with DEA license management and reporting, pedigree lot tracking, brand and generic inventory, warehouse management, sales force automation, business intelligence, and more. **Vormittag Associates,** *Ronkonkoma, NY • www.vai.net • tel. 800.824.7776*

MISCELLANEOUS

Drug-storage system

WireCrafters' Drug Enforcement Agency (DEA)-Approved Storage Brochure shows how WireCrafters Style 840 Partitions meet or exceed DEA special requirements for storage of Schedule III–V controlled substances. Its secured-storage system is designed to be cost-effective. **WireCrafters,** *Louisville, KY • www.wirecrafters.com • tel. 800.626.1816*

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Report From Russia – *contin. from page 50*

services for public and municipal needs" (5). These regulations (6) are designed to combat abuse arising in the course of public procurement of medicines in connection with combining several INN (international nonproprietary names) within one lot, especially for cases where the lot contains a certain drug for which exclusive vertical agreement with distributor was made. For example, the distributor may purchase the whole lot of an innovated drug for a maximum price without having any competition at all.

Advertising and other means of control

Another important issue is the advertising of medicines and medical products. Recently, this subject has been brought up for discussion during parliament hearings of the Committee on protecting the health of State Duma of the Russian Federation. Plans for implementing stringent provisions on advertising medicines have been announced more than once on the level of Russian Government and State Duma.

FAS clarified, in one of its letters issued in the summer of 2012, the current ban for advertising of prescription medicines and the respective exceptions for advertising on the Internet. Discussions are currently underway on how the advertising of medicines and medical products should become more regulated.

Conclusion

In conclusion, there is an escalation of public control and regulation affecting the pharmaceutical industry in Russia. Such escalation highlights the necessity to bring the industry to the highest international standards, regulate uncontrolled market growth, protect competition, and ensure compliance with international practice, so that the Russian market will appear favorable to foreign investors in view of the country's WTO accession last year. However, there is concern that legislators may have missed the fact that stricter governmental control over the industry could also have a negative effect because market access will become more difficult and perhaps impossible for foreign and domestic SMEs or new market players.

References

1. Government Regulations on Decree, "On licensing pharmaceutical activity" No. 1081, Dec. 4, 2012.
2. State Duma Federal Law, "On licensing certain types of activities" FL No. 99, July 28 2012 version with amendments valid as of Jan. 1, 2013.
3. State Duma Federal Law, "On circulation of drugs" FL No. 61, June 25, 2012 version, item 6 of Art. 18.
4. State Duma Federal Law, "On fundamental healthcare principles in the Russian Federation" FL No 323, June 6, 2012 version, Art. 74.
5. State Duma Federal Law, "On allocation of orders for supply of goods, execution of works and rendering of services for public and municipal needs" FL No. 94, version of Dec. 30, 2012.
6. FAS, Ministry of Healthcare, Draft Regulations "On establishing threshold value of the initial (maximum) contract value (lot value), at the increase of which different drugs bearing INN (or in absence of INN, bearing chemical group names) cannot be subject to one contract (one lot)" as of Oct 12, 2012. **PT**

Ad Index

The Effect of FDASIA on Inspections

David Elder, vice-president, technical at PAREXEL, discusses how US legislation allows for inspection of generic-drug activities.

Q. How will the new FDASIA user fees affect inspections?

A. On July 9, 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA). This legislation passed both the House and Senate with overwhelming bipartisan majorities, signifying an effective, cooperative legislation process that included FDA, Congress, patients, doctors, and the pharmaceutical and medical device industries.

The legislation is intended to provide FDA with added resources and authorities required to bring drugs and devices to market safely and quickly and promote innovation in the biomedical industry. In addition to the reauthorization of the Prescription Drug User Fee Act (PDUFA V) and the Medical Device User Fee and Modernization Act (MDUFMA III), it authorizes user fees for generic drugs and biosimilars. The Act establishes new initiatives, requirements, and authorities in other key areas as well and is certainly worth a careful study by its stakeholders.

The legislation includes explicit provisions relating to inspections but, in addition, it is important to understand the commitments made by FDA during the legislation negotiation time that will also drive implementation. When viewed collectively, I believe that the greatest impact of the new legislation to inspections will be in the area of generic drugs.

The Generic Drug User Fee Act (GDUFA), Title III of FDASIA, authorizes the agency to collect user fees to supplement the agency's cost for conducting human generic-drug activities. Unlike the legacy user fee acts, GDUFA specifically defines covered FDA activities to include facility inspections. FDA has committed to conducting risk-adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in fiscal year (FY) 2017. One of the specific provisions in GDUFA is the requirement for sites to self-identify, which will provide FDA with a more complete and up-to-date inventory of generic-drug establishments.

With a better inventory of generic-drug establishments, the ability to allocate user fees to conduct inspections, a mandate to achieve inspection frequency parity among domestic and foreign establishments, a mandate for FDA to annually report year-to-year inspection metrics, and newly defined risk factors that include time since the last inspection, compliance history, and inherent product risk (see FDASIA Section 705), FDA is poised to significantly escalate the number of generic-drug inspections worldwide.

The greatest impact of the new legislation to inspections will be in the area of generic drugs.

This legislation also provides FDA with additional authorities that facilitate and augment its inspection program:

- Under FDASIA Section 706, drug establishments must provide FDA, upon request, any records FDA would be entitled to obtain during an on-site inspection
- Under FDASIA Section 707, drugs will be deemed misbranded if a drug establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection
- Under FDASIA Section 712, FDA may rely upon the inspections of capable foreign government agencies and may protect information received from foreign government agencies from disclosure under the Freedom of Information Act (FDASIA Section 708)
- Under FDASIA Section 718, there is now extraterritorial jurisdiction over any violation of the law if the drug or other regulated article was intended for import into the United States or if any act in furtherance of the violation was committed in the US. **PT**

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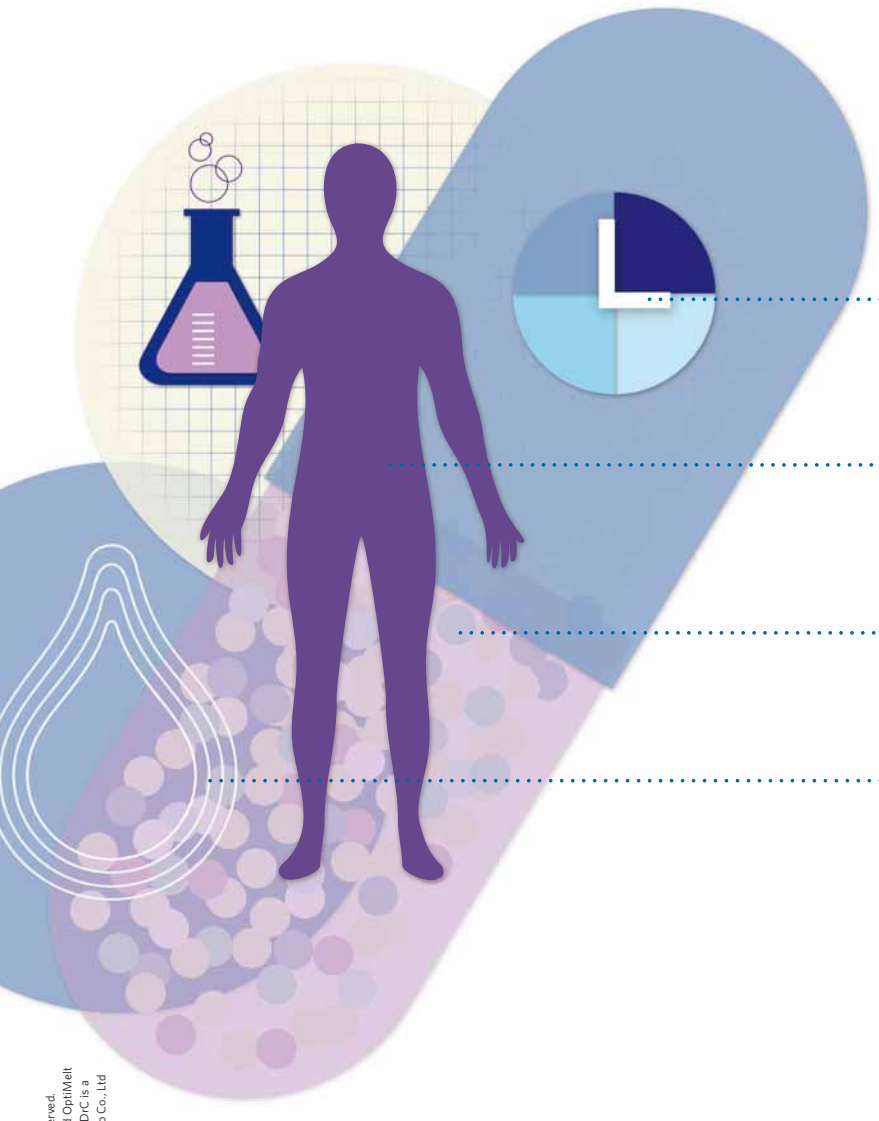

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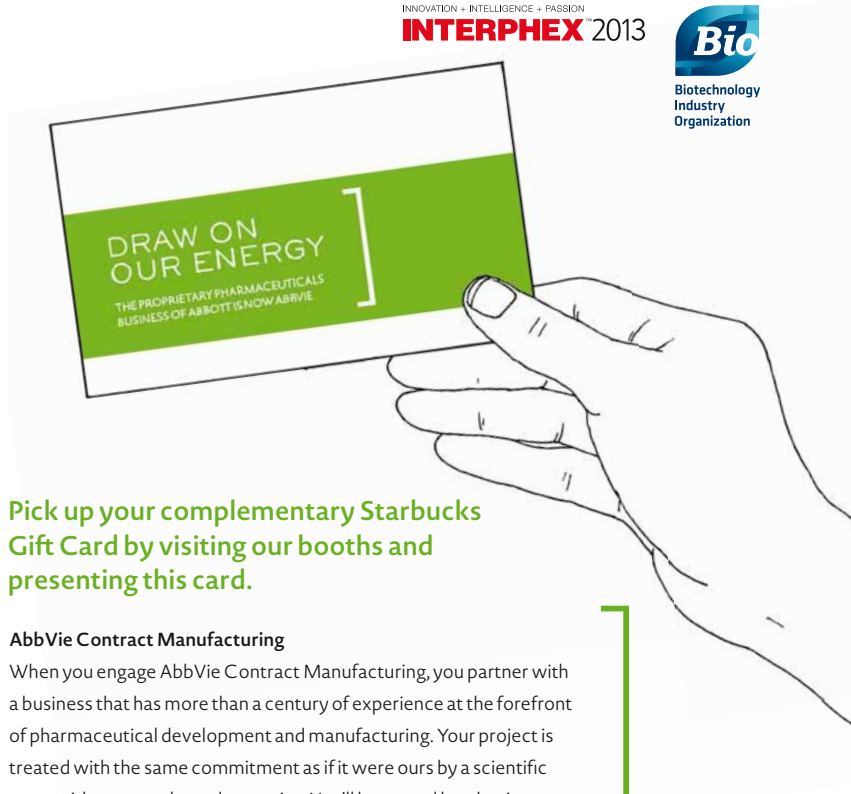

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