SEPTEMBER 2013 Volume 37 Number 9

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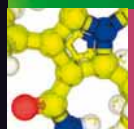

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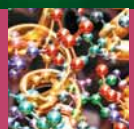

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COVER STORY

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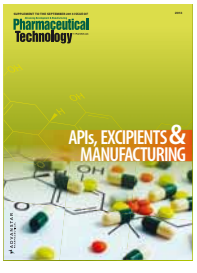
SUPPLEMENT

Be sure to check out this month's API, Excipient, and Manufacturing special issue featuring articles on taste masking, quality by design, risk assessments for excipients, and more.



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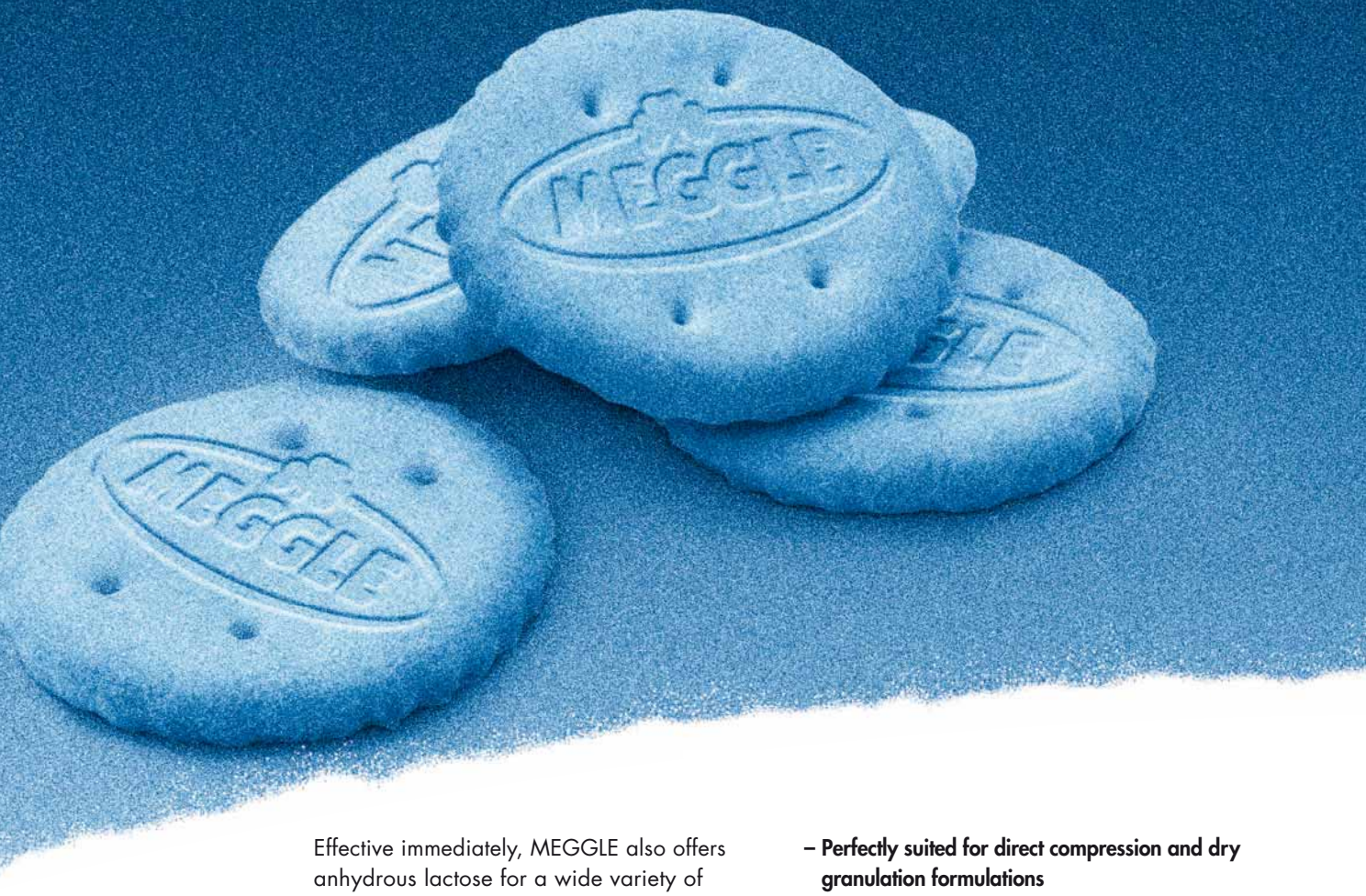

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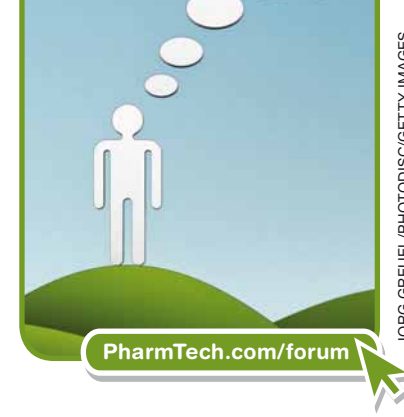

JORG GREUEL/PHOTODISC/GETTY IMAGES

Connecting People, Science, and Regulation

Richard Johnson

PDA/FDA regulatory conference promotes a commitment to quality.

The Parenteral Drug Association (PDA) focuses on connecting people, science, and regulation. For more than 60 years, PDA members have been active in responding to and driving implementation of global regulatory initiatives. Association members did not recently discover what the "c" in cGMP stands for; they have been actively defining and shaping it for many years. Nowhere is this commitment and energy more in evidence than at the annual PDA/FDA Joint Regulatory Conference, which will be held for the 23rd year, on Sept. 16–18 in Washington, D.C.

An objecive indentified in PDA's Strategic Plan—Regulation—states: "Our regulatory activities are scientifically and technically focused, and current information is communicated to our members."

The organization supports this strategy with several criteria, including:

- The provision of science- and technology-based input on regulations and guidelines related to PDA strategic areas, utilizing PDA's volunteer and membership base
- Maintaining valuable and effective relationships with global regulators and educating members on current expectations.

Richard Johnson is president of the Parenteral Drug Association (PDA).

Over the past six decades, PDA members have commented on every key cGMP regulation and guidance. PDA has hosted joint conferences with regulators, provided specialized training to regulatory authorities, and included regulatory officials in its processes for developing technical reports. This activity led to the creation of the PDA/FDA Joint Regulatory Conference nearly 25 years ago.

It did not take long for this conference to become one of the most important annual events hosted by PDA for its members. Overall meeting attendance and the number of attendees and speakers representing not just FDA, but regulatory bodies from around the world has grown each year.

The 2013 PDA/FDA Joint Regulatory Conference: Driving Quality and Compliance throughout the Product Life Cycle in a Global Regulatory Environment, opens with a business imperative. Janet Woodcock, MD, director of FDA's Center for Drug Evaluation and Research (CDER) will provide regulatory perspective, and Daniel Kraft, MD, executive director of FutureMed, will provide industry insight on the status of quality systems, quality by design, and drug shortages. The conference will conclude with information about FDA initiatives from representatives of CDER, the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA).

The conference offers four plenary sessions:

- The Quality Culture & Partners session explores ways to implement quality culture, how the culture impacts the effectiveness of a quality system, and highlights significant indicators of a weak quality culture.
- In the Understanding Good Manufacturing Practices session, speakers will discuss how safety and efficacy is assured by routine adherence to the quality assurance and manufacturing control practices embodied in the GMPs.
- A Patient's Perspective is designed to offer insight from a patient—someone who can help drug development professionals focus on their mission by expressing how drug products have helped save lives.
- In the Compliance Update session, compliance directors at each FDA center will report on current topics in the compliance arena.

Following the conference, on Sept. 18–19, there's a session you will want to attend: the 2013 PDA/FDA Improving Investigations Workshop. FDA specialists and industry experts discuss the root causes of poor investigations. As you may know, these are among the top inspection observations globally. Finally, extend your learning in one of six courses offered by PDA's Training and Research Institute.

These activities exemplify PDA's tireless focus on "Connecting People, Science, and Regulation." **PT**

Editors' Picks of Pharmaceutical Science & Technology Innovations

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Omega Design Corporation Introduces LabelSync 450

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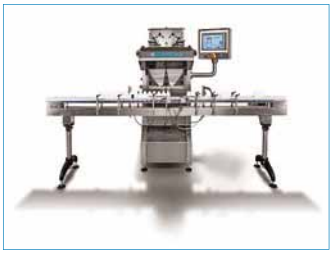

Bosspak VTC 100 Tablet and Capsule Counter

The Bosspak VTC 100 electronic tablet and capsule counter from Romaco's is designed to fill pharmaceutical solids or food supplements into bottles at high speed. The machine works independently of particular formats, allowing the product and packaging to be changed quickly. The tablets, caplets, or gelatine capsules are fed to the counting stations by means of vibratory feed trays. The new sensor generation features built-in microprocessors that adjust the count trigger point automatically during production. The Bosspak VTC 100's pre-dosing system can improve both counting accuracy and filling speed. The machine counts a maximum of 100 bottles a minute and can be installed either as a standalone unit or integrated in a line.

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FDA Works to Secure Drug Supply Chain

New policies aim to strengthen inspection and oversight processes.

Key to implementing the FDA Safety and Innovation Act (FDASIA) of 2012 is for FDA to issue new regulations and guidance that will help manufacturers understand how the agency aims to strengthen oversight of today's global drug industry. Title VII of FDASIA provides added authority for FDA to inspect drug-production facilities; to block import of adulterated and substandard medical products; to require adherence to manufacturing standards; and to crack down on violators.

All manufacturing establishments now have to register with FDA.

Agency leaders marked the first anniversary of FDASIA at a public meeting on July 12, 2013. The meeting updated industry on how the new policies will affect operations and ensure a more level playing field between suppliers and manufacturers at home and abroad. It also gave all parties an opportunity to comment on agency proposals for strengthening FDA authority over drug imports. FDA commissioner Margaret Hamburg opened the meeting by noting the importance of collaborative efforts with other regulators, with industry, and with crucial stakeholders in better securing a "more complex and more global supply chain." Most notable was her announcement of a new proposed rule and a draft guidance document, the first of several such documents required to flesh out the FDASIA policies.

John Taylor, counselor to the commissioner and now acting deputy commissioner for global regulatory operations and policy, similarly noted the vast increase in countries, importers, and foreign facilities that produce FDA-regulated therapies. Title VII provides FDA with stronger tools to use against firms that refuse inspections or seek to import noncompliant products. And stiffer penalties for drug counterfeiting have been authorized by the US Sentencing Commission to go into effect in November 2013.

Additional data and information on facilities and operations will support a more effective system for targeting inspections and oversight of imports. These data are important for implementing Title VII's various programs and requirements, explained Susan de Mars, senior advisor to the Office of Global Regulatory Operations & Policy. All manufacturing establishments now have to register with FDA and provide unique facility identifiers (UFIs) that will populate an electronic database able to track manufacturer operations, identify importer compliance, and generate information related to lost, stolen, or counterfeit products.

FDASIA's provisions enhance partnerships and collaboration with foreign regulators, making it easier for FDA to exchange confidential information with peer regulators. The agency gains flexibility to recognize or rely on inspections of other regulators, which can help extend FDA's limited resources, de Mars noted. FDA has been engaged in several inspection collaborations, and the legislation should lead to more formal recognition and mutual reliance on foreign government inspection findings.

Inspections intensified

A key FDASIA goal is to strengthen FDA's authority to inspect manufacturing facilities in the US and abroad. By eliminating the traditional requirement that FDA inspect domestic drug facilities every two years, the legislation supports a shift to a risk-based inspection system that targets high-risk firms. FDASIA also authorizes FDA to examine facility records electronically and in advance of a site visit, which can help the agency determine whether or not to actually conduct the inspection at that time.

If FDA determines during an inspection that certain drugs may be adulterated or misbranded, it now can detain those products, instead of waiting for a court order to do so, which can give unscrupulous operators a chance to distribute the violative products. FDA describes how it will implement this new policy in a proposed regulation, which is similar to the policy already in force for medical devices and food (1).

New draft guidance further clarifies how FDA plans to conduct full and complete inspections of factories, warehouses, and other facilities involved in drug production (2). The guidance spells out how firms that delay, deny access, or limit inspections may have their products deemed misbranded and adulterated and not fit for sale in the US. The document lists prohibited behaviors that could delay the scheduling of inspections or an inspection in process, such as failure to produce requested records in a timely manner. And it spells out how manufacturers can run into trouble by preventing an inspector from beginning or completing a site visit. FDA specifies that its agents have the right to access and copy records and to collect product samples as needed, including samples of finished products, raw materials, in-process materials, reserve samples, and environmental samples.

One notable paragraph states that FDA inspectors have authority to photograph facility conditions, an issue that has been the subject of heated legal debate for years. Lawyers already are questioning whether FDASIA actually does permit agency officials to use cameras during an inspection, and Doug Farquhar of Hyman, Phelps & McNamara speculates in the *FDA Law Blog* whether a company that refuses to permit photography will end up as a test case in court (3). FDA would like to receive comments on the guidance by Sept. 13, 2013.

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Overseeing imports

A main purpose of the July public meeting was to provide manufacturers and other stakeholders with an opportunity to comment on FDA proposals for setting standards for imports, for registering commercial importers, and for devising good importer practices (GIPs). FDA expects GIPs to address registration requirements for commercial importers, exemptions (possibly for research products) to importer regulation, and the importance of importers meeting broader compliance standards, such as GMPs or demonstrating a satisfactory inspection history. One issue, noted FDA senior policy advisor Brian Pendleton, is whether importers should be required to establish drug safety management programs as part of GIPs.

There was discussion about how useful a certificate of analysis is in documenting product authenticity, or if these forms are too easily falsified. The United States Pharmacopeia Convention (USP) proposed that compendia standards serve as a key marker for importer compliance. Excipient producers requested an exemption from import restrictions, noting that foreign producers ship large quantities of excipients to the US for a broad range of uses, making it impossible to segregate out those products specific to pharmaceutical production.

Another important topic is whether to permit compliant importers to qualify for expedited clearance procedures. US manufacturers would like to see risk-based standards for those importers that meet high standards, noted Sarah Spurgeon, assistant general counsel at the Pharmaceutical Research and Manufacturers of America (PhRMA). Industry representatives also proposed that GIP requirements might differ based on the type of drug imported, company inspection history, and evidence of supply-chain controls.

The globalization of drug production is a positive development, in that manufacturers can make products anywhere and market them worldwide via the Internet, noted John Taylor. But FDA "can't just do more inspections and more examinations of imports," he said. Instead, the agency needs to engage in inter-agency activities within the US and collaborate more with international regulatory and health organizations. FDA will be issuing a number of regulations and guidance documents to implement its new programs and is looking for manufacturers to help weigh all the options.

Reference

1. *Federal Register,* Vol. 78, No. 135, pp. 42382-6 (July 15, 2013).
2. FDA, *Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection*, draft guidance (July 12, 2013), http://www.fda.gov/RegulatoryInformation/Guidances/ucm122044.htm, accessed Aug. 2, 2013.
3. Farquhar, www.fdalawblog.net (July 18, 2013). **PT**

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EU Raises API Standards: A Curse in Disguise?

The aim of the newly enacted European Falsified Medicines Directive is to improve the quality of imported APIs, but does the pain now outweigh the gain?

The number of substandard pharmaceutical ingredients coming into the EU has increased in recent years; however, when the European Commission (EC) first revealed details of the implementation of new EU rules for GMP standards for imported APIs, both the pharmaceutical industry and regulators warned about the potential dangers of these restrictions in causing medicines shortages. The new regulation, part of the EU's Falsified Medicines Directive (FMD), requires that imports of APIs into the EU must be accompanied with written confirmation by a national regulatory authority that the manufacturing plant complies with GMP standards. This requirement has raised concerns that the importation of a large proportion of APIs would be severely hampered as a result. And yet, six weeks after the new rules came into effect on July 2, 2013, there has been no evidence of any major upheaval in the supplies of APIs in the EU—approximately 70% of which are imported, with 60% of these imports coming from India and China.

"Currently, we have not been notified of any critical disruption of API supplies, or manufacture of medicinal products, linked to the enforcement of the new EU rules on the importation of active substances," a spokesperson for the EC told *Pharmaceutical Technology.* The European Federation of Pharmaceutical Industries and Associations (EFPIA), the main trade body for research-based pharmaceutical companies, also confirmed that it had not yet received any reports from its members about any immediate difficulties with imported API supplies after July 2. An EFPIA official, however, informed *Pharmaceutical Technology* that "it is too early to assess properly the impact of the new system."

Exemption from written confirmation

To date, four countries (i.e., US, Japan, Australia, and Switzerland, which is a non-EU country) have been excluded from the requirement for written confirmation on grounds that their regulatory and monitoring standards on GMP are equivalent to those of the EU. Several other countries, including Brazil, Mexico, Singapore, and Israel, have applied to be exempted, or to have previous refusals of exemptions reviewed, according to the EC. The regulation also enables the authorities in the EU's 28 member states to apply various waivers when implementing the written confirmation requirement. If, for example, an API plant has already been inspected and given a GMP certification by EU inspectors, written confirmation may be considered to be unnecessary.

Nonetheless, exactly how the new rules are being applied in individual EU countries has been unclear because of delays in including the FMD regulations in national statutes. By early August, eight of the 28 member states were yet to transpose the written confirmation obligation into their laws. In other countries, the implementation date has been held back. For example, in the UK, the requirement was not in full effect until August 20.

In most countries, the checking of whether an imported API is accompanied by a written confirmation is left to the individual pharmaceutical manufacturers. Without the confirmation, a medicine with the imported API cannot be marketed legally in the EU. "(We) will monitor compliance with the rules in relation to finished-product manufacturers as well as companies importing active substances," explained the Danish Health and Medicines Authority in a statement on the new rules (1). "The Danish customs authorities will not check whether the import rules have been observed." On the other hand, countries, such as Spain, are verifying compliance through import controls at their borders while Germany and the Netherlands are planning to do the same.

Alternative suppliers

Some manufacturers were quick to react to the possibility of new restrictions on imported APIs at the time when the FMD was being debated in the European Parliament and the European Council representing EU governments. They signed deals with alternative API suppliers with GMP certification, particularly those based in the EU. "In a recent survey of our members, we found that many of them had been asked by European pharmaceutical companies to become second-source suppliers of their active substances," said Tony Scott, advisor to the European Fine Chemicals Group (EFCG), representing EU producers of APIs.

National licensing authorities have been working closely with their countries' pharmaceutical manufacturers to pinpoint API sources that may have difficulties complying with the new EU restrictions. Risk assessments of potentially problematic active ingredients have been carried out. These assessments investigate reasons for the absence of written confirmations, levels of existing stocks of the APIs with the medicine manufacturers, and the availability of alternative products and treatments. "(We are) aware of 107 risk assessments being carried out by member states although it is highly likely that many more have been done," says an official at the European Medicines Agency (EMA). EMA has been monitoring the implementation of the written confirmation requirement.

On the basis of the results of the risk assessments, national authorities have been helping pharmaceutical companies to take precautionary measures. "Some API sources for UK finished-product manufacturers were (shown to be) potentially at risk," a spokesperson for the UK Medicines and Healthcare Products Regulatory Agency (MHRA) told *Pharmaceutical Technology.* "However, further analysis by the manufacturers showed that such risks could be mitigated, for example, by stocks being held and the use of alternatives from approved

API sources. The situation is being kept under review by MHRA at a UK level and by the weekly meetings at an EU level."

Due to concerns about possible medicines shortages in the short to medium term, EU regulators have been prioritizing inspections of some non-approved plants outside Europe by EU GMP inspectors. "(We know) of 12 future planned inspections of sites for which no written confirmation is available although some of these inspections may ultimately not be necessary as more non-EU authorities start issuing written confirmations," the EMA official told *Pharmaceutical Technology*. "In addition, EMA is aware of three EU inspections that have been carried out although it is highly likely that there have been more."

India and China step up GMP standards

In the longer term, EU regulators are hoping that India and China, which between them have more than 900 sites exporting APIs to Europe, will establish comprehensive and reliable GMP inspection systems that will eliminate the problem of certification of exported active substances. In India, the Central Drugs Standard Control Organization (CDSCO), part of the country's Ministry of Health and Family Welfare, has been issuing written confirmations. Details of the confirmation with names of the APIs are available on the CDSCO website.

China only began issuing written confirmations this spring through the Chinese Food and Drug Administration (CFDA), which supervises GMP inspections but only in pharmaceutical plants. It has no responsibility for GMP standards in chemical plants making and exporting APIs. "China is a very big country so there are difficulties with quality standards in APIs production while there is also a need for harmonization of GMP inspections," commented Stefan Kettelhold, lead auditor at Germany's blue inspection body GmbH, which does a lot of auditing work in China. "The Chinese government used to concentrate on raising production standards of companies supplying the domestic market. With the new legislation, it is also focusing on GMP of API suppliers for the international market. The Chinese authorities want to see a general upgrading of standards in pharmaceuticals."

One likely result of tougher domestic and international regulations on production standards in India and China will be a consolidation among API manufacturers. There will be fewer of them, but they will be able to ensure that their active substances are of a more consistently acceptable quality than at present.

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The Elements of Training

Establishing a well-defined training program that ensures employees have the appropriate combination of knowledge, skills, and experience to perform their job functions is a crucial activity for any organization.

Training represents one of the key elements that management can use to assure a consistent, high quality, product. Codifying the elements of the training program will help a company maintain compliance to the regulations and address regulatory concerns about employee qualifications that might arise during inspections. Some companies are fortunate to have either a training department or a training coordinator to define and administer the program. Companies that do not have either should establish a training team with representatives from the quality assurance, quality control, and operations departments at a minimum. There should be approximately four parts to any training program: the introductory training requirements for new employees, the annual training requirements for all employees regardless of function, the continuing education training expectations, and special training requirements that may be required for continuous quality and process improvements. The first three may be tracked with a training matrix.

Introductory training requirements

New employees should be initially trained on applicable GMPs, good documentation practices (GDPs), and any additional global requirements impacting their jobs. It is prudent for a company to develop a quiz or test to demonstrate the new employee's comprehension of these basic requirements with an established minimum passing percentage. The minimum percentage must be achieved before the employee is considered to have the basic knowledge needed to work in the company. Incorrect answers should be discussed as part of the process. If the required minimum is not achieved, the prospective employee should be provided additional instruction on the material and a different test should be employed to measure comprehension. If the minimum required comprehension level is still not achieved, the quality assurance department should inform the hiring manager and indicate the new employee is not suitable for employment. Once new employees have passed the minimum understanding requirements on the quizzes, they should then be trained on company policies and specific job-related standard operating procedures (SOPs).

Annual training requirements

Companies should perform annual refresher training on a variety of topics. At a minimum, it is recommended that employees be retrained annually on cGMPs and cGDPs. Additional yearly training topics could be tailored to the type of operations being conducted at the facility. If the company is manufacturing parenteral products, the annual training program might include modules on microbiological control in aseptic manufacturing and conducting investigations/root cause analysis. This yearly training should also measure employee comprehension of the material. This comprehension might be measured in a variety of ways including but not limited to written quizzes, oral quizzes, and hands-on demonstration. Whichever way is chosen to assess the employee's comprehension of the material, it should be noted on individual training records.

Continuing education training requirements

Employees should be encouraged to enhance their job-specific knowledge and skills by attending external training conferences, seminars, and activities. The training team should be responsible for reviewing literature and recommending which employees should attend specific courses to enhance their skills and knowledge. The benefits of the external training should be discussed with senior management. There are several organizations that provide seminars, training classes, and symposia including the American Society for Quality, the Parenteral Drug Association, the American Chemical Society, and for-profit organizations.

Special training

Companies need to recognize there may be occasions when special training is required for employees. The responsibility for determining the need for special training will reside with the training team but should be performed using qualified trainers with recognized expertise in the specific discipline being addressed. Using qualified trainers in this situation assures the attendees will be trained by experts that will understand questions that may arise during training. As with all training, a record of the training should be put into the employee's personnel folder.

When a company invests in the future of its employees by establishing a comprehensive training program, they need evidence that the monies were well spent. To assure continued funding for training, management should establish metrics to monitor performance as a practical measure of the ongoing effectiveness of training activities. By continuing to invest in training, companies invest in their employee's futures and develop a knowledgeable, skilled, and experienced workplace as well as a culture supporting continual improvement and growth. **PT**

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EMERGING MARKET REPORT

Report from: Brazil

Hellen Berger

Pharma eyes biologics production in Brazil as the government begins to recognize the potential of these drugs.

In Brazil, there are indications that the pharmaceutical industry has been living relatively comfortably despite global difficulties. Due to improved wages and jobs created over the past few years, thousands of Brazilians who never had access to drugs have been investing in healthcare and purchasing medicines, not only to treat illnesses but also as a means of prevention.

According to the Brazilian Association of National Laboratories Distributors (Abradilan), figures from IMS Health show that sales of pharmaceutical drugs in Brazil are expected to rise 15–20% this year compared to (Brazilian Real) R$49.6 billion (approximately US$21.6 billion) in 2012. The Gross National Product (GNP) for 2013 is expected to be 2.28% higher this year, according to Brazil's Central Bank.

In 2011, the so-called "C class," which represents 53% of the 200-million population in Brazil, contributed to 42% of the domestic sales of pharmaceutical drugs in 2011, while the wealthy "A and B classes" were responsible for 48% of total sales, according to IMS Health. Companies operating in Brazil are beginning to understand that it is important to target the middle class as they outnumber the wealthier classes and are willing to pay for all types of goods, including pharmaceuticals. As a result, production of pharmaceutical drugs is on the rise despite the high costs and taxes in Brazil. Investment plans, however, are ongoing with opportunities seen ahead, especially for biological drugs.

Government plans include local production

Biological drugs are cellular- or tissue-based medical products. They include, among others, vaccines, blood components, and living cells used to treat various diseases. The production is mainly though gene-modification processes, rather than synthetic. Producers have reported that biological drugs have greater accuracy to treat illnesses according to the Industry Syndicate of Pharmaceutical Products in the State of São Paulo (Sindusfarma).

In an interview with *Pharmaceutical Technology*, Nelson Mussolini, executive president for Sindusfarma, said that "there is no doubt that biological drugs have great potential in Brazil. They will add to other drugs offered by the country's public health system to treat illnesses such as rheumatoid arthritis, asthma, and various types of cancer. This fact can be proven by the actions developed by the Brazilian government to implement local production of biological drugs, through its Health Ministry and the Bank of Economic and Social Development (BNDES)."

According to Mussolini, Sindusfarma associates correspond to more than 90% of Brazil's pharmaceutical market share, hosting companies that promote both national and international research as well as commercialize biologics and biosimilar products. "The health ministry would guarantee purchasing these drugs under the public health system and the BNDES would guarantee funding and financing for research and production of biological products," added Mussolini.

The topic of biologics production has definitely caught the interest of policy makers, and the pharmaceutical industry sees it as an opportunity given that the government in Brazil is developing the biologics market. The Brazilian government strongly supports research partnerships in this field and is encouraging local production of biological drugs. According to Sindusfarma, the government is willing to pay as much as 25% more for locally produced biological drugs compared to what it pays for imported products.

Mussolini noted that while Argentina is also taking steps to localize production of biologics, Brazil will likely be the main

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player in Latin America for these products because of its growing pharmaceutical market. Although the biologics market is in its infancy and, therefore, specific figures are difficult to obtain, investments in this area have already been officially confirmed.

New production facility confirmed

Novartis told *Pharmaceutical Technology* that the company will be building a new facility to produce biological drugs in Brazil. The Swiss pharmaceutical company will invest R$1 billion (approximately US$ 435 million) in a unit located in Jaboatão dos Guararapes, in the Northeastern state of Pernambuco, to produce vaccines against Hepatitis B.

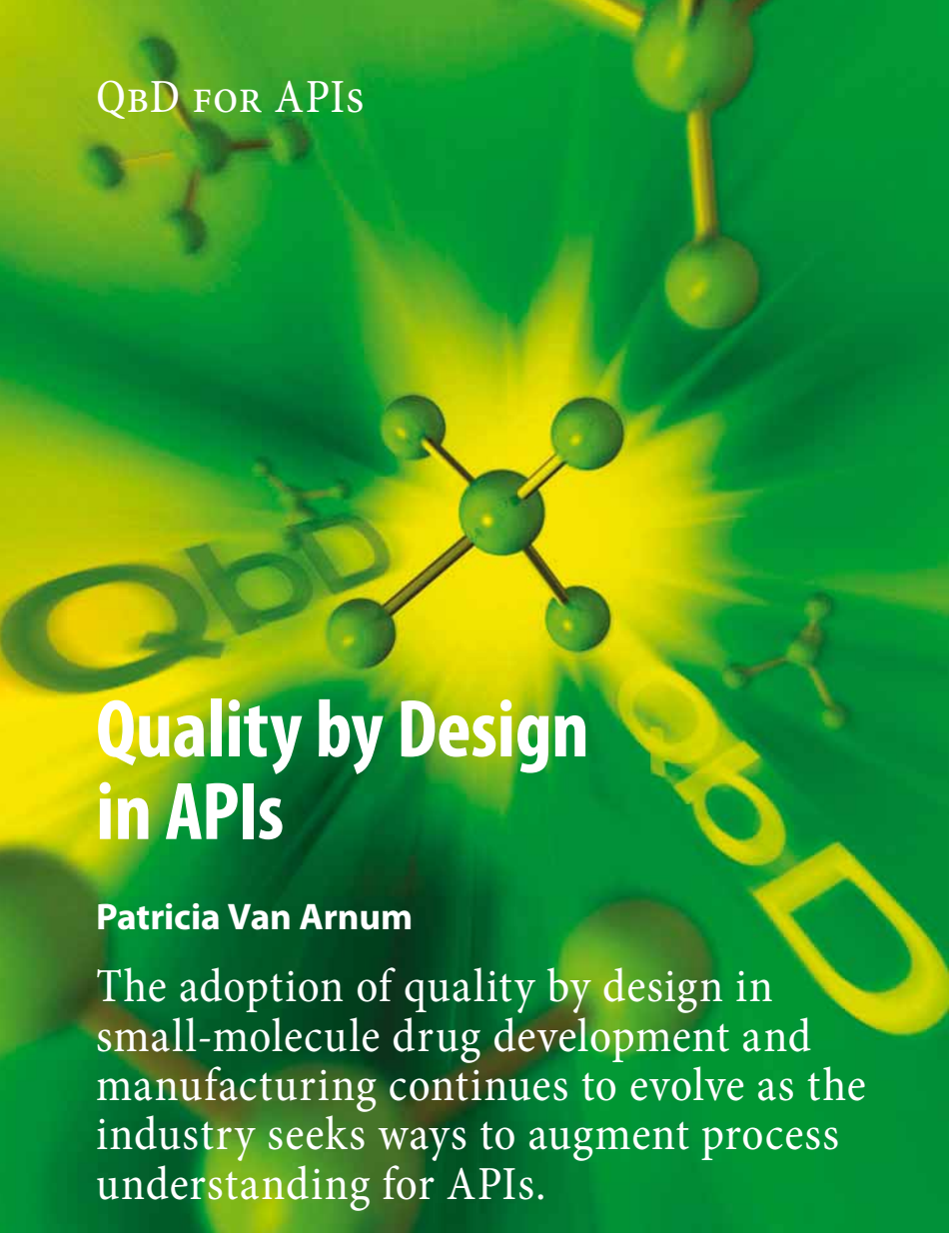
Novartis Brazil said this plant will be the company's first vaccine production site in Latin America. Construction is expected to be completed by June 2014, while production has been scheduled to start in 2016 according to the company.

According to Novartis, the company plans to export part of its vaccines output from the new plant and gradually transform the unit into a full-scale biologics producer. Novartis and Brazil's federal government have signed transfer-of-technology (TOT) deals to produce drugs in government-owned facilities, hence, making the country less dependent on imported products and technologies.

Novartis is not the only company to sign TOT deals with the federal government. The country's health ministry stated that it is negotiating approximately 27 deals with public and private laboratories to produce as many as 14 biological drugs nationally. The ministry's objective is to increase the number of locally produced biological drugs for the treatment of breast cancer, leukemia, rheumatoid arthritis, and diabetes among others. According to government figures, the country would save around R$225 million (approximately US$ 97.8 million) a year with local production, using transferred state-of-the-art technology. With so many incentives, perhaps many other eyes will soon turn to the biological products market in Brazil. **PT**

The government is willing to pay as much as 25% more for locally produced biological drugs compared to what it pays for imported products.

*— **Hellen Berger** is a business news correspondent based in São Paulo, Brazil.*



Quality by Design in APIs

Patricia Van Arnum

The adoption of quality by design in small-molecule drug development and manufacturing continues to evolve as the industry seeks ways to augment process understanding for APIs.

The science- and risk-based approach in quality by design (QbD) entails greater product and process understanding as a means to ensure product quality. These concepts are embodied in ICH guidelines Q8 (R2) *Pharmaceutical Development*, Q9 *Quality Risk Management*, Q10 *Pharmaceutical Quality System*, and most recently, Q11 *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* (1–4), which offer a lifecycle approach to continual improvement to drug manufacturing.

Traditional versus enhanced approaches

ICH Q11 focuses specifically on the development and manufacture of drug substances. It specifies that a company can follow "traditional" or "enhanced" approaches or a combination of both in developing a drug substance (4). In the traditional approach, set points and operating ranges for process parameters are defined, and the drug-substance control strategy is typically based on process reproducibility and testing to meet established acceptance criteria (4). In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that affect critical quality attributes (CQAs) (4). The enhanced approach further includes the development of appropriate control strategies applicable over the lifecycle of the drug substance that may include the establishment of design space(s) (4). Manufacturing process development should include, at a minimum, according to ICH Q11:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on drug-product quality can be studied and controlled
- Defining an appropriate manufacturing process
- Defining a control strategy to ensure process performance and drug-substance quality (4).

An enhanced approach to manufacturing process development would additionally include:

- A systematic approach to evaluating, understanding, and refining the manufacturing process, including identifying—through prior knowledge, experimentation and risk assessment—the material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters that can have an effect on drug-substance CQAs
- Determining the functional relationships that link material attributes and process parameters to drug-substance CQAs (4).

The enhanced approach, in combination with quality risk management, is used to establish an appropriate control strategy. Those material attributes and process parameters important to drug-substance quality should be addressed by the control strategy. The risk assessment can include an assessment of manufacturing process capability, attribute detectability, and severity of impact as they relate to drug-substance quality (4). For example, when assessing the link between an impurity in a raw material or intermediate and drug-substance CQAs, the ability of the drug-substance manufacturing process to remove that impurity or its derivatives should be considered in the assessment (4). The risk related to impurities can usually be controlled by specifications for raw material/intermediates and/or robust purification capability in downstream steps. It is important to understand the formation, fate (whether the impurity reacts and changes its chemical structure), and purge (whether the impurity is removed via crystallization, extrac-

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tion, etc.) as well as their relationship to the resulting impurities that end up in the drug substance as CQAs (4). The process should be evaluated to establish appropriate controls for impurities as they progress through multiple process operations (4).

Regulatory expectations

In March 2011, the European Medicines Agency and Food and Drug Administration launched a three-year pilot program for a parallel assessment by both agencies of certain quality and chemistry, manufacturing and control (CMC) sections of new drug applications submitted to FDA and marketing authorization applications (MAAs) submitted to EMA that are relevant to QbD, such as development, design space, and real-time release testing. The objective of the pilot, which is scheduled to end Mar. 31, 2014, is to ensure consistent implementation between the European Union and the United States of ICH guidelines Q8, Q9, Q10, and Q 11 and to facilitate sharing of regulatory decisions (5–7).

In August 2013, the agencies reported that the first EMA–FDA parallel assessment of QbD elements of an initial MAA was successfully finalized as well as some consultative advice procedures. In a question-and-answer format, EMA and FDA reported on their expectations as they relate to quality target product profiles (QTPPs), CQAs, classification of criticality, and application of QbD in analytical method development (7).

With respect to the QTPP, the agencies specified that they expect applicants to provide the QTPP, which describes prospectively the quality characteristics of a drug product that should be achieved to ensure the desired quality, safety, and efficacy of the drug product. With respect to CQAs, the agencies expect applicants to provide a list of CQAs for the drug substance, finished product, and excipients when relevant. This list should also include the acceptance limits for each CQA and a rationale for designating these properties as a CQA. Furthermore, there should be a discussion of how the drug substance and excipient CQAs relate to the finished product CQAs based on prior knowledge, risk assessment, or experimental data. The basis of the control strategy is to ensure that the drug substance and finished product CQAs are consistently within the specified limits (7).

Those material attributes and process parameters that are found to be important to drug-substance quality should be addressed by the control strategy.

Another issue was whether the agencies would accept a three-tier classification of criticality for process parameters. The agencies responded that ICH Q8 (R2) specifies that a critical process parameter is one whose variability has an impact on a CQA and needs to be monitored or controlled to ensure the process produces the desired quality. EMA and FDA cited a regulatory submission in which the applicant proposed an approach to risk assessment and determination of criticality that included a three-tier classification ("critical," "key," and "noncritical") for quality attributes and process parameters. Using this classification, a "critical" factor was defined as a factor that led to failure during experimentation. A factor that had not led to failure within the range studied, but still may have an impact on product quality, was considered as a "key" factor. The agencies said that they do not support the use of the term "key process parameters (KPP)" because it is not ICH terminology and there is differing use of the term "key" among applicants. Although FDA and EMA said they are amenable to this terminology in the pharmaceutical development section to communicate development findings, they are not in describing the manufacturing process, process control, and control of critical steps and intermediates, where the description of all parameters that have an impact on a CQA should be classified as critical (7).

The agencies further specified that process manufacturing descriptions be comprehensive and describe process steps in a sequential manner, including batch size(s) and equipment type. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified (7). Steps in the process should have the necessary detail in terms of appropriate process parameters along with their target values or ranges. The process parameters that are included in the manufacturing process description should not be restricted to the critical ones; all parameters that have been demonstrated during development as needing to be controlled or monitored during the process to ensure that the product is of the intended quality need to be described (7).

The agencies also commented on QbD as it relates to analytical methods using risk assessments and statistically designed experiments to define analytical target profiles (ATP) and method operational design ranges (MODR) for analytical methods (7). "There is currently no international consensus on the definition of ATP and MODR," noted the agencies. "Until this is achieved, any application that includes such proposals will be evaluated on a case-by-case basis" (7). The agencies noted, however, that an ATP can be acceptable as a qualifier of the expected method performance by analogy to the QTPP as defined in ICH Q8 (R2), but the agencies would not consider analytical methods that have different principles (e.g., high-performance liquid chromatography and near-infrared [NIR] spectroscopy) equivalent solely on the basis of conformance with the ATP. "An applicant should not switch between these two types of methods without appropriate regulatory submission and approval," they said. The agencies also noted that

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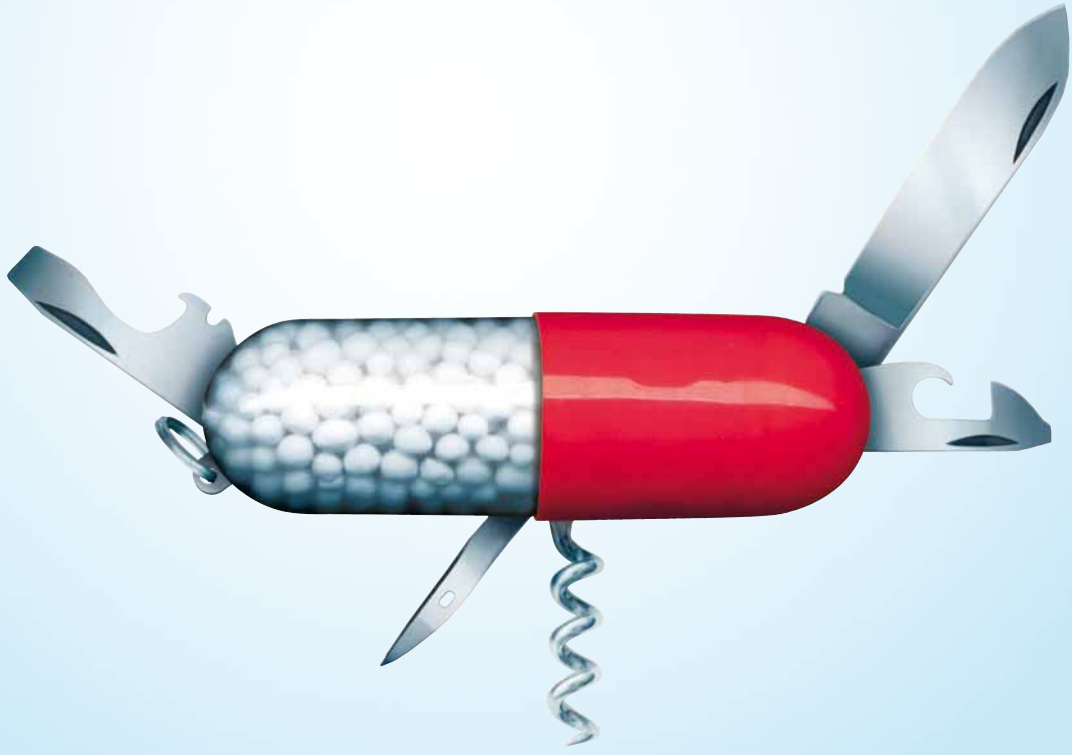

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similar principles and data requirements could apply for MODRs. For example, data to support an MODR could include: appropriately chosen experimental protocols to support the proposed operating ranges/conditions and demonstration of statistical confidence throughout the MODR. Issues for further reflection include the assessment of validation requirements as identified in ICH Q2 (R1) throughout the MODR and confirmation of system suitability across all areas of the MODR (7). The agencies further indicated that future assessment of the pilot program will include other lessons learned in areas such as design-space verification, the level of detail in submissions for design space and risk assessment, continuous process verification, and continuous manufacturing.

In August 2013, FDA and the European Medicines Agency reported on lessons learned from an EMA–FDA parallel assessment of QbD elements examined from submissions in their pilot program.

QbD at work

A review of recent literaure reveals some interesting applications of QbD in drug-substance development and manufacturing. For example, scientists at Bristol-Myers Squibb reported on a process-modeling method using a QbD approach in the development of the API ibipinabant, a cannabinoid receptor 1 antagonist being developed to treat obesity (8). In its development, the molecule had volume requirements of 6 kg for toxicology studies and formulation development, which later increased to 175 kg for late-stage clinical trials. The researchers used mechanistic kinetic modeling to understand and control undesired degradation of enantiomeric purity during API crystallization. They implemented a work flow, along with kinetic and thermodynamic process models, to support the underlying QbD approach and reported on the use of risk assessment, target quality specifications, operating conditions for scale-up, and plant control capabilities to develop a process design space (8). Subsequent analysis of process throughput and yield defined the target operating conditions and normal operating ranges for a specific pilot-plant implementation. Model predictions were verified from results obtained in the laboratory and at the pilot-plant scale (8). Future efforts were focused on increasing fundamental process knowledge, improving model confidence, and using a risk-based approach to re-evaluate the design space and select operating conditions for the future scale-up (8).

Scientists at Merck & Co. reported on their work in applying QbD to set up an improved control strategy for the final five steps in the production route of a legacy steroidal contraceptive, which has been produced for more than 20 years within its facilities (9). A generic ultra-high-performance liquid chromatography method was developed according to QbD principles to create a range of proven acceptance criteria for the assay and side-product determination for the final five steps in the production route of the API (9).

Scientists at Eli Lilly reported on a systematic approach consisting of a combination of first-principles modeling and experimentation for the scale-up from bench to pilot-plant scale to estimate the process performance at different scales and study the sensitivity of a process to operational parameters, such as heat-transfer driving force, solvent recycle, and removed fraction of volatiles (10). This approach was used to predict process outcomes at the laboratory and pilot-plant scale and to gain a better understanding of the process. The model was also used further to map the design space (10).

In other work, scientists reported on the application of latent variables-based modeling to a reaction process in a small-molecule synthesis based on continuous-flow hydrogenation (11). In another study, scientists reported on using a QbD approach for designing improved stability studies (12). Also, scientists at UCB and the Institut des Sciences Moléculaires de Marseille in France recently reported on the feasibility of using online NIR spectroscopy as a process analytical technology tool to monitor in real time the API and residual solvent content to control the seeding of an API crystallization process at industrial scale. A quantitative method was developed at laboratory scale using statistical design of experiments and multivariate data analysis (13).

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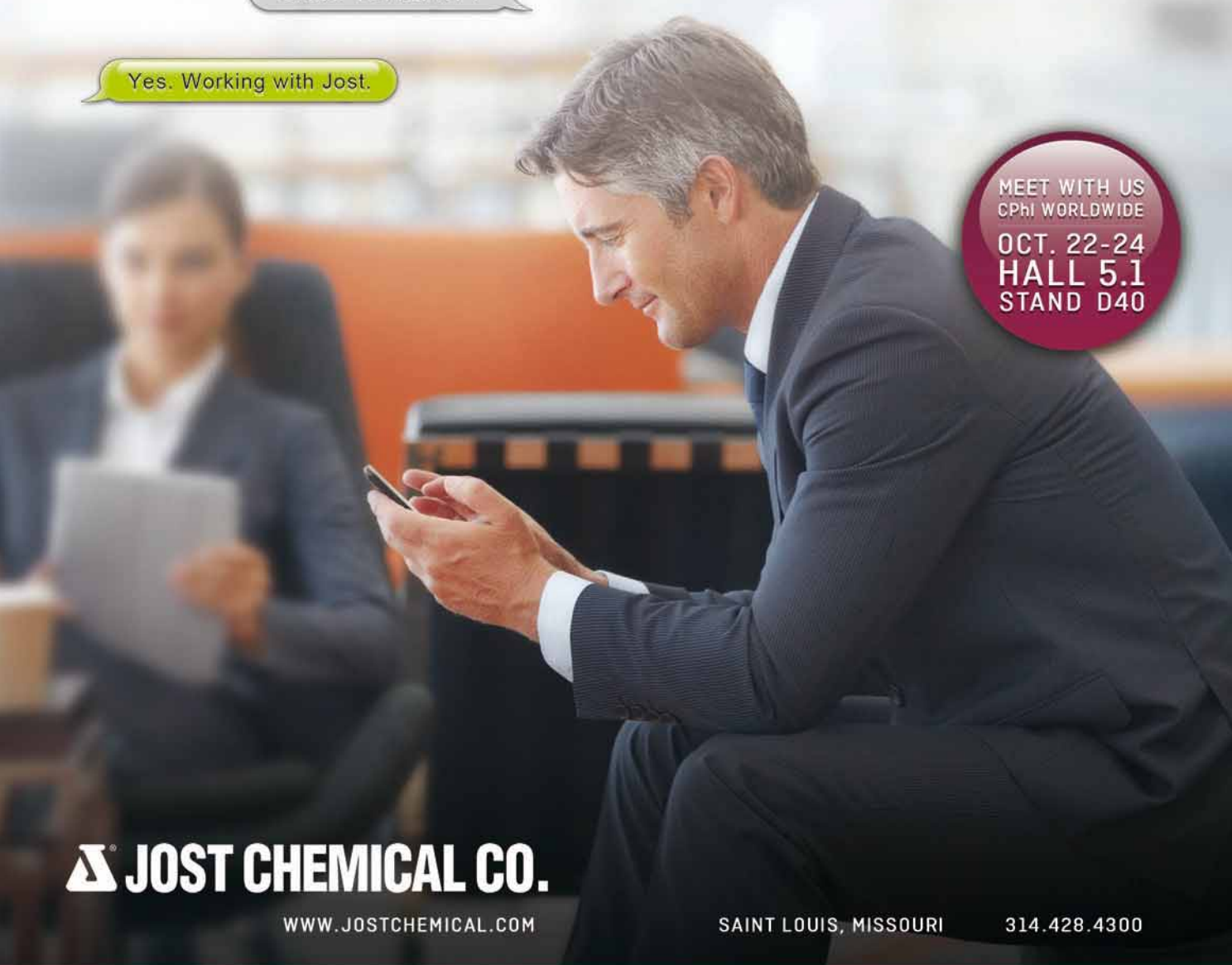

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The Importance of Characterization in Biosimilars Development

An industry roundtable moderated by Adeline Siew, PhD

Industry experts discuss the requirements and challenges involved in getting a biosimilar product from bench to launch.

The global market for biosimilar drugs has been forecasted to be worth $2.445 billion in 2013 (1). The growth corresponds to a 20% increase from last year's figures and accounts for approximately 2% of the overall biologics market (1). Although narrowly focused on only a few therapy areas at present, the biosimilars market is set to expand over the next decade and beyond as a result of two major factors: the impending patent expiries on blockbuster biologics and the financial crisis that is driving payers to push for wider adoption of biosimilars to manage the escalating costs of healthcare.

Many companies are keen on getting a share in the biosimilars market given its promising outlook; however, bringing these complex molecules from bench to launch can be a challenge, not just during the development stage but also in terms of the manufacturing process involved. *Pharmaceutical Technology* conducted a roundtable to gain further insight on this topic. Participants included: Sheen-Chung Chow, PhD, professor, Department of Biostatistics and Bioinformatics at Duke University School of Medicine; Christina Satterwhite, PhD, director of laboratory sciences, Charles River Laboratories; Fiona Greer, PhD, global director, biopharma services development, Bruno Speder, team leader of clinical trial regulatory affairs, Clinical Research, and Rabia Hidi, PhD, director of biomarkers & biopharmaceutical testing, Laboratory Services, all three at Life Sciences Services at SGS.

The complex nature of biosimilars

PharmTech: Why are biosimilars not approved in the same way as generics?

Sheen-Chung Chow, PhD, professor, Department of Biostatistics and Bioinformatics, Duke University School of Medicine

Chow (Duke University): The regulatory approval pathway is well established for generic drugs; however, it cannot be applied to biosimilars due to fundamental differences between generic drugs and biosimilars. For example, generic drugs are small-molecule drug products that contain 'identical' active ingredient(s) as the branded drug. Biosimilars, on the other hand, are made of living cells or living organisms that are sensitive to environmental factors such as light and temperature during the manufacturing process. Biosimilars usually have mixed and complicated structures that are difficult, if not impossible, to characterize. As a result, biosimilars are not generic drugs.

Fiona Greer, PhD, global director, biopharma services development, SGS

Greer (SGS): Biosimilar drugs cannot be regarded in the same way as generics. The exact structure of small-molecule synthetic drugs and their impurities can be well defined chemically, which enables generic manufacturers to avoid full, costly clinical studies if they are able to establish that their product is 'bioequivalent' in pharmacokinetic studies to the branded or listed drug. However, unlike small-molecule drugs, biologically derived products are large, complex protein molecules, usually comprising of a mixture of closely related species that undergo post-translational modifications, which influence the anticipated protein structure. When produced in mammalian expression systems, these proteins can also be glycosylated (i.e., the carbohydrate is attached to the protein backbone), thereby, further increasing the amount of heterogeneity in the glycoforms produced.

In addition, the complexities of cellular expression and biomanufacturing make exact replication of the originator's mole-cule nearly impossible; the process will certainly be different. Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants, or post-translational modifications (e.g., the glycosylation profile) can be significantly altered by changes, which may initially be considered to be 'minor' in the manufacturing process, but can greatly affect the safety and efficacy profiles of these products. Biosimilars are, therefore, not simple generics. The fundamental difference with complex protein molecules is that they cannot be absolutely identical to the original. Instead, companies developing these 'copies' must demonstrate that they are similar by performing a side-by-side comparison with reference samples of the originator.

FOTOSEARCH/GETTY IMAGES

Christina Satterwhite, PhD, director of laboratory sciences, Charles River

Satterwhite (Charles River): Biosimilars are not approved in the same way as generics because they are similar but not identical to the original biological products due to the manufacturing processes used to generate these types of molecules. A biosimilar is a biologically derived product that can have subtle structural differences with each manufacturing process, which may result in different properties.

The road to approval

PharmTech: Can you describe the legal and regulatory approval pathways for biosimilars in Europe and the United States?

Bruno Speder, team leader of clinical trial regulatory affairs, Clinical Research, SGS

Speder (SGS): Both the European and US regulatory pathways depend on being able to demonstrate 'biosimilarity' involving rigorous comparison against batches of originator product, initially at the physicochemical level, then in a step-wise manner in safety, potency, and clinical studies. Only an originator product that was licensed on the basis of a full registration dossier can serve as a reference product (i.e., centralized procedure in Europe and new drug application in the US). Both in Europe and the US, extensive consultation with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), respectively, is required.

Greer (SGS): The European Union established the first legal regulatory guidelines for 'similar biological medicinal products' (i.e., biosimilars) (2–4). Subsequently, specific product annexes were published (5). Several of the original guidelines have been, or are in the process of being, revised. The first biosimilar molecule approved in Europe in April 2006 was Omnitrope, a version of somatropin. All guidelines, plus current revision concept papers and drafts, are available on the EMA website (5).

Meanwhile, in the US, the Biologics Price Competition and Innovation Act (BPCIA) provides a new pathway for biosimilars—the 351(k) route of the Public Health Service (PHS) Act. This pathway also requires comparison of a biosimilar molecule to a single reference product that has been approved under the normal 351(a) route with reference to prior findings on safety, purity, and potency. In contrast, one aspect of the legislation unique to the US is the provision for two levels of product—'biosimilar' and 'interchangeable biosimilar.' An interchangeable biological product is one that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. Therefore, more data are required for a product to be labeled as interchangeable rather than biosimilar.

In February 2012, FDA published three draft guidance documents to assist biosimilar developers: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (6), *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* (7) and *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (8). Earlier this year, a fourth guidance, dealing with scientific meetings, was issued (9).

Satterwhite (Charles River): The EU has developed a science-based regulatory guidance framework from 2005 to the present to ensure high-quality biosimilar drugs. The biosimilars pathway in the US was created under the *Patient Protection and Affordable Care Act* in 2010 (10); however, US regulations are still pending. Three draft guidances (6–8) were released in February 2012 with a focus on the analytical characterization and totality of evidence approach to the program. A fourth draft guidance (9) was released in 2013 that emphasized formal meetings between the sponsor and regulators. Many pharmaceutical and biotechnology companies are moving forward using the International Conference on Harmonization (ICH) and FDA regulatory guidances currently governing biologic submissions and strategies that incorporate the EU biosimilar regulatory guidance. Although the draft guidance is available, there remains some confusion within the industry.

Bioequivalence testing

PharmTech: Can you explain the procedures for testing the bioequivalence of biosimilars and how it differs from bioequivalence testing for generic drugs?

Chow (Duke University): The current regulation for approval of generic-drug products is based on testing for average bioequivalence. For assessment of biosimilars, it is suggested that testing for biosimilarity should focus on variability rather than average bioavailability alone. Besides, it has been criticized that the one-size-fits-all criterion is not appropriate for assessment of biosimilars.

Satterwhite (Charles River): One of the major differences in the testing of biosimilars as opposed to generics is that the drug-development package must not only test structure but also function. A biosimilar program should commence with a strong analytical package that typically incorporates the testing of protein quantity and purity, amino-acid sequence, glycosylation, physicochemical properties, and aggregation analysis. Lot release and stability testing should also be incorporated. In addition, these properties need to be known for the originator drug and multiple lots of the originator drug should, therefore, be evaluated. The type of functional tests evaluated should be based on the mechanism of action of the drug. For example, an anti-CD20 monoclonal antibody may include the following assessments: antibody-dependent cell-mediated cytotoxicity (ADCC) assay, complement dependent cytotoxicity (CDC) assay, flow-cytometry apoptosis assay, flow-cytometry binding assay, and Fc receptor assays.

Speder (SGS): Testing the bioequivalence of biosimilars differs from that of standard generics, both in the nonclinical testing as well as in the design of the clinical studies. The bioequivalence of generics is compared in a randomized, two-period, two-sequence, single-dose, crossover-design study. The treatment periods should be separated by a wash-out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally, at least five elimination half-lives are necessary to achieve this. In

most cases, no nonclinical studies need to be conducted on the generic product.

For biosimilars, most of which have long half-lives, a crossover study would be ineffective and unethical due to the fact that the wash-out period would be quite long. The patient is not allowed to take the drug during this wash-out period, and hence, will have no treatment for his/her condition. Therefore, parallel-group studies are required, but these studies do not provide an estimate of within-subject variation. For biosimilars, extensive head-to-head nonclinical testing with the originator product is required.

Similarity is difficult to establish as different manufacturing processes can result in differences in glycosylation sites as well as aggregates.—*Satterwhite*

Characterization studies

PharmTech: Why is structural and functional characterization especially important for biosimilars?

Satterwhite (Charles River): The analytical packages that are required for a robust program should be conducted prior to any *in-vivo* testing. The structural *in-vitro* tests, along with the functional *in-vitro* tests, provide necessary information to assess the biosimilarity of the molecules. Similarity is difficult to establish as different manufacturing processes can result in differences in glycosylation sites as well as aggregates. It is important that analytical tests, including structural and functional characterization, provide data in which subtle differences are revealed and risk assessment is conducted prior to continuing to the next step in the development program.

Greer (SGS): The development pathway for a biosimilar is unlike that of a novel biotherapeutic. Undoubtedly, there is an increased requirement for analytics. This enhanced analytical effort, which may be rewarded in the reduced requirement for clinical trials, entails initial physical, chemical, and biological characterization of the biosimilar in comparison to the originator reference product. If found to be 'similar' during this extensive characterization, subsequent nonclinical and clinical data are then required to demonstrate the same safety and efficacy profiles as the originator compound. However, the premise is that the amount of nonclinical and clinical data required will be much less than for a novel stand-alone application, and generally, a Phase II trial is not necessary. Extensive studies should, therefore, be conducted to provide comparative data for the biosimilar side-by-side with the originator. Strategies at this stage must include assessment of primary and higher-order structure as well as batch-to-batch variation for the biosimilar and the reference product. In practice, analytical characterization will follow the requirements of the ICH guideline Q6B (11), including determination of amino-acid sequence, post-translational modifications, including disulfide bridges and glycosylation, and spectroscopic profiles.

One of the most important analytical techniques for biomolecule structural characterization is mass spectrometry (MS). Usually several different types of instruments are used in the detailed study of a glycoprotein so that the overall structure can be elucidated, including electrospray–mass spectrometry (ES–MS), online ES–MS where the MS is coupled to a high-performance liquid chromatography (HPLC), matrix-assisted laser-desorption ionization–mass spectrometry (MALDI–MS), and for derivatized carbohydrates, gas chromatography–mass spectrometry (GC–MS). Apart from the ability to study nonprotein modifications such as sulfation and phosphorylation, the other major strength of an MS approach is in the analysis of mixtures, which has obvious applications in the analysis of heterogeneous glycoforms.

The objective of the comparative study is to establish whether the biosimilar has the same primary protein sequence of amino acids as the reference product. This can be done by using classical protein sequencing (automated Edman degradation), peptide MS-mapping, MS/MS sequencing, and amino-acid analysis.

For products that are glycosylated, characterization of the carbohydrate structure is essential too. Glycosylation is arguably the most important of the numerous post-translational modifications, but what is undeniable is that it presents a unique challenge for analytical methods. The population of sugar units attached to individual glycosylation sites on any protein will depend on the host cell type used, but it will be a mixture of different glycoforms on the same polypeptide. Powerful MS-based strategies can be used to analyze both free (i.e., underivatized) and derivatized samples to determine sites of glycosylation of both N- and O-linked structures, the identity of terminal nonreducing ends (potentially the most antigenic structures), and the types of oligosaccharide present. Chromatographic anion-exchange methods can also be used for glycan

Biosimilars development and supply: how complex can the process be?

The increasing demand for good-quality healthcare comes with the challenge of controlling healthcare expenditure. Biosimilars offer the potential of increasing access to much-needed biologic medicines for patients at a reduced cost, but as this new class of therapeutics is introduced into healthcare systems worldwide, there must be an uncompromising commitment to patient safety, which starts with high regulatory approval standards and ongoing manufacturer accountability. In this article, Martin Van Trieste, senior vice-president of quality at Amgen, explains how the development and supply of these complex molecules is not only scientifically challenging but also capital intensive. Developing a high-quality biologic medicine that is safe and effective requires a commitment to manufacturing excellence and innovator companies often need to invest up billions to bring a biologic product to market.

The full article is available at: **PharmTech.com/biosimilars_MartinVanTrieste**

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DAY ONE, TUESDAY, OCTOBER 22, 2013

12:00 *Main Conference Registration*

1:00 *Chairman's Welcome and Opening Remarks*
Ivan Soto, Associate Director QA Validation & Computer Systems, **Alexion Pharmaceuticals, Inc.**

1:15 **Video Conference**

FDA Regulatory Trends, Warning Letters and Enforcement Actions Related to Process Validation

In January 2011, the FDA finalized and published revisions to the guidance "Process Validation: General Principles and Practices". As industry navigates the process validation lifecycle, more knowledge is gained towards full process understanding. This session focuses on information, case studies, and lessons learned from the two years since guidance finalization, and how industry and the Agency are adjusting to the new process validation paradigm.

- Update to FDA's Process Validation Guidance — 2 years later
- Insights on FDA's compliance and enforcement strategy
- Global regulatory trends and outlook
- Inspection planning and readiness
- Remediation in response to FDA enforcement

Steven Hertz, M.S., M.B.A., Consumer Safety Officer, **CDER, FDA** *(invited)*

1:55

Ripped from the Headlines — Process Validation Landmines & Pitfalls

Process validation is a continuous process calling for planned lifecycle management to ensure that the manufacturing process is capable, sustainable and consistent. This is achieved through the systematic collection, and analysis of product and process-related data, against the history of actions enacted throughout the lifecycle of the product. The often experienced tyranny of validation is almost always a result of not employing a lifecycle approach to process validation, for new or legacy products.
This session addresses:

- What's hot and what's not in FDA's world of process validation
- How to implement a lifecycle approach pre and post commercialization
- What does FDA expect?
- How does one measure success?

Carmen Medina, M.P.H, Ph.D. (c), Vice President Technical, **PAREXEL International** *(former FDA investigator)*
Paula Brockmeyer, Principal Consultant, **PAREXEL International**

2:40

Strategically Communicate with Both Internal and External Stakeholders to Ensure a Smooth Audit and Inspection Process

Effective communication with both internal and external stakeholders is critical in navigating a successful FDA inspection. It is integral to understand the important role of strategic communication to be taken prior, during and after an FDA inspection. This session provides an in-depth, practical look at the following:

- Prepare internal stakeholders for a FDA inspection
- Handle out of the ordinary requests from FDA inspectors
- Communicate with the FDA should a dispute arise during the course of the FDA inspection
- Suggestions on how to communicate with the FDA during the closeout meeting

Sonali P. Gunawardhana, Of Counsel, FDA Practice Group, **Wiley Rein LLP;** *Former Regulatory Counsel, Office of Compliance,* **FDA/CDRH**

3:20 *Networking and Refreshment Break*

3:50

Cost Effective Lifecycle Validation Management

The lifecycle concept of product and process management together with continual improvement is here to stay. No more magic "three batches and I'm done" as a validation paradigm. GMP regulations, guidelines and expectations are changing at an astonishing pace. This session takes a look at the challenges of managing a closely scrutinized budget and delivering validation packages that meet requirements. At the end of this session, participants understand how a genuine validation management system works to reduce waste and enhance quality. Value added activities versus "make nice" and a corporate culture of improvement discussed are together with what constitutes a "smart" validation package.

- Define validation requirements
- Risk assessment from the perspective of validating what is most likely to fail
- Write smart validation protocols (do what matters and explain why)
- Avoid waste in validation programs
- Assess validation costs and the costs of non-compliance

Karen S. Ginsbury, B.Pharm, M.Sc, MRPharmS, President, **PCI Pharmaceutical Consulting, Israel Ltd**

4:30

Reduce Risks and Costs of Laboratory Equipment Qualification — A Global Approach

This session analyzes recent FDA audit results and latest trends to identify areas of highest risk in the instrument lifecycle and then suggest strategies to focus limited resources to help ensure your regulated lab stays in compliance while reducing costs and system downtime. Explore key considerations and benefits of automation in today's instrument qualification in light of:

- Regulatory trends
- Aspects of Analytical Instrument Qualification (AIQ)
- Review of FDA Warning Letters
- Implement validation processes globally

Gary Powers, Global Compliance Program Manager, **Agilent Technologies, Inc.**

5:10

Understand the Interdependency between Change Control and Validation

- Quality Systems — CAPA, change control, investigations and validation
- How change control needs validation
- Document and verify changes effectively
- How validation needs change control

Justin Roose, Senior Validation Engineer, **Amway**

5:40 *Close of Day One*

Please join us for a Networking Wine and Cheese Reception immediately following the final session.

DAY TWO, WEDNESDAY, OCTOBER 23, 2013

7:30 Continental Breakfast hosted by QPHARMA

7:30 EYE-OPENER Breakfast Discussion

Method Validation — Develop Processes that Survive the Lifecycle

I. Test Method Validation Expectations
- Regulations and guidance
- Good science
- Management buy-in at all levels

II. Method Validation Implementation
- Method validation as it relates to the product lifecycle
- The quality plan
- The design/development/control loop
- Definition of intended use
- Selection of characteristics and acceptance

Jerry Lanese, Ph.D., President, **The Lanese Group, Inc.**

8:30 – 10:00 Choose Between Four 90-minute Sessions (1-4)

SESSION 1: Process Validation Lifecycle Management — Principles, Policies and Practice

I. Process Validation as a Product Lifecycle Management Program
- FDA's most current landscape
- Why this works
- FDA's expectations
- Industry trends
- Trending programs and how they impact your process

II. Prepare for the Future
- Pre-requisites for a validation product lifecycle management approach
- Old versus new products
- Synergize with risk assessment
- Infrastructure requirements

III. Define the Beginning and the End
- What should be monitored and why
- Value drivers
- Risk trending
- Re-contextualize management mindsets

IV. Key Drivers for FDA Compliance
- Current FDA trends
- Regulatory overview
- FDA 2011 Guidance for the Industry
- CPG Sec. 490.100

V. Measure Success
- The quality triad
- The GEM Plan™
- Establishing alert & action limits

VI. Interactive Exercise — Design Your Product Lifecycle Management Approach
Attendees should expect to discuss their vision for designing a meaningful approach for both new and legacy products.

Carmen Medina, M.P.H, Ph.D. (c), V.P. Technical, **PAREXEL International** *(former FDA investigator)*

Paula Brockmeyer, Principal Consultant, **PAREXEL International**

SESSION 2: Quality by Design — The Path to Lean Validation

ADVANCED

I. What Is QbD?
- Quality target product profile
- Critical Process Parameters (CPP) vs. key parameters and parameters
- Critical Quality Attributes (CQA) and other attributes
- Controlling and reducing variability
- Process Performance Qualification (PPQ) — Process understood and reproducible
- Continued Process Verification (CPV) — Reduced sampling faster

II. Design of Experiments
- Popcorn in the microwave
- Proven Acceptable Range (PAR)
- Design space

III. Interactive Exercise
Participants work to identify critical process parameters and their effect on critical attributes after defining the target product profile and using facilitated brainstorming to identify potential factors causing variability, and discuss PPQ and CPV.

Karen S. Ginsbury, B.Pharm, M.Sc., MRPharmS, President, **PCI Pharmaceutical Consulting, Israel Ltd.**

Session 3: Good Practices for Computerized Systems in GxP Environment — PIC/S Guidance

In January 2011, FDA became a member of PIC/S. As a member, FDA participates as PIC/S partners to share global vision. This includes how to be collaborative, and fully productive as part of international GxP inspectorate enterprise to create a safety net that ensures drug quality worldwide. Therefore, PIC/S guidance is considered by FDA to achieve this goal. One of PIC/S guidance is PI 011-3 "Good Practices for Computerized Systems in Regulated GxP Environment".

I. The Guidance Structure
- What is the history?
- What are the sections?
- What each section contains?

II. Key Concepts
- Define the "computerized system"
- Good practices — From implementation to operation
- Inspection considerations

III. Regulation and Industry
- How the guidance aligns with other regulations and guidelines
- How the guidance addresses the supplier quality management system

IV. Interactive Exercise
Attendees complete a questionnaire used for inspection of computerized system.

Mehron Mirian, B.S., QA Senior Computer System Validation, **B.Braun**

SESSION 4: Planning and Executing a Process Validation Study

MEDICAL DEVICE

I. Overview of the Process Validation and Validation Planning

- Identify and define the intended use of the equipment and processes for the validation
- Perform risk assessments for the equipment, facilities and processes
- Planning validation/verification activities using a Master Validation Plan

II. Execute a Process Validation Study

- Perform and document equipment and facilities qualifications
- Determine Critical Process Parameters (CPP) of the processes to be validated
- Statistical techniques
- Perform and document the process validations and deviation handling
- Write the validation reports and other technical documentation
- Establish process monitoring activities and documentation

III. Interactive Exercise

Using a real-life scenario, participants study how to plan and perform a validation for a multi-bottle filling and labeling system and packaging system in a new environmentally controlled room while preparing validation documentation.

* Bonus Material

- Examples of Master Validation Plan, Validation Protocol and Validation Report

J. Sean Osso, Senior Systems Engineer and Global Process Owner of Validation, **Dako Corporation, an Agilent Technologies Company**

10:00 Networking Refreshment Break

10:30 – 12:00 Choose Between Four 90-minute Sessions (5-8)

SESSION 5: Writing Effective Validation Protocols, Execution and Results

I. Introduction to Validation Protocols

- Goals of protocols
- Standard practices

II. Develop Protocols

- The importance of a good template
- Writing tester instructions
- Writing "expected results"

III. Execute Protocols

- Who and how

IV. Document Results

- Objective evidence — How much is enough?
- Documenting deviations

V. Interactive Exercise

In this exercise, attendees are presented with a set of requirements from which they are to develop, execute and document brief test protocols, using the knowledge gained from the workshop.

Joseph Zec, Senior Validation Manager, Quality & Regulatory, **Philips Healthcare**

SESSION 6: Senior-level Think Tank — Strategies for the Advanced Validation Professional

ADVANCED

In this closed-door summit, senior level validation and quality managers from pharmaceutical, biotech and medical device companies engage in open discussions with colleagues about strategies for managing their most pressing challenges. The content for the summit is driven by the participants, who are surveyed ahead of time about the topics they wish to discuss.

This session is open to the first twenty senior-level professionals who pre-register for the workshop. In order to pre-register, you must have over 5 years experience in validation execution and currently work for a pharmaceutical, medical device or biotech company.

Ivan Soto, Associate Director QA Validation & Computer Systems , **Alexion Pharmaceuticals, Inc.**

SESSION 7: Best Practices for a Robust Cleaning Validation Program

I. Identify Risk

- Understand your soils
- Components of cleaning chemistry
- Select sampling locations and methods
- What problem areas to look for

II. Develop Meaningful Acceptance Limits

- Calculate residue limits
- Determine limits for cleaning agents
- What is visually clean and how clean is clean?
- Things to avoid in setting limits
- Determine hold times

III. Perform a Risk Assessment

- Best practices for product grouping
- Conduct a risk assessment

IV. Interactive Exercise

Participants troubleshoot actual cases where validated processes eventually failed or validation protocols failed to determine root cause and corrective actions and discuss how to mitigate such failures.

Beth Kroeger, Technical Services Specialist, **STERIS Corporation**

SESSION 8: Conduct Prospective Validation

MEDICAL DEVICE

I. Medical Device Process Validation
- Why, how and when
- Best practice for medical device
- Tools and templates

II. Process Validation Lifecycle for Medical Device
- Validation stages — A lifecycle approach
- Incorporate process design phase into validation documentation
- Process Qualification (PQ) phase
- Continuous Process Verification (CPV) phase

III. Interactive Exercise
Participants apply techniques covered during this session to create a risk based validation plan and procedures to determine validation acceptance.

Jacalyn Schroeder, Quality Engineering Specialist, **3M Company**

12:00 Awards Luncheon Hosted by **Agilent Technologies**

1:30-3:00 Choose Between Four 90-minute Sessions (9-12)

SESSION 9: Lean Validation — Reduce Costs in the Computerized System Validation Process

I. Faster, Leaner, Compliant Computer System Validation
- Remove non-value added and redundant activities
- Integration and streamlining of the process
- Meet minimum regulatory requirements

II. Establish a Cost Effective and Compliant Framework
- Standardization of a systematic approach
- Establishing a lifecycle framework to improve integration of processes
- Risk-Based approach to reduce cost and effort

III. Interactive Exercise — Eliminate Rework
Participants use real world experience to identify the areas that cause rework within the computer system validation activities and determine what possible solution(s) could be implemented to eliminate rework and reduce cost.

Gregory W. Pierce, President, **EngiSystems**

SESSION 10: Showing Your Quality System to the Inspector — How to Successfully Navigate a GMP Inspection

I. Getting Ready
- Prepare the company for a regulatory inspection
- The opening meeting — Concise, precise, useful to the inspector

II. The Inspection
- How to manage the process
- Professional — Rapid document retrieval; Subject Matter Experts (SMEs)
- Careful attention to the questions — Responses provide the information the inspector is looking for
- Do's and don'ts

III. Close-Out
- Wrap-up meeting
- Timely and carefully composed response to findings
- Follow up on commitments

IV. Interactive Exercise
Case studies — Questions for the class to answer and role play for do's and don'ts in an inspection.

Karen S. Ginsbury, B.Pharm, M.Sc., MRPharmS, President, **PCI Pharmaceutical Consulting, Israel**

SESSION 11: Qualification and Routine Environmental Monitoring of Critical Utility Systems Qualification

I. Qualification Phase for Utility Systems
- Use the SIA and CCA results to support the writing of IQ and OQ protocols
- Leverage the FAT and SAT to support the writing of IQ and OQ protocols

II. Performance Qualification Phase for Utility Systems
- Structure the PQ protocols to meet the various testing phases (Phase I, II, and III)
- Establish acceptance criteria and regulatory agency expectations

III. Routine Environmental Program for Utility Systems
- Develop a routine environmental monitoring program
- Develop risk-based routine sampling procedure for each utility system
- Utilize the trended data from the PQ protocol to establish alert and action levels

IV. Trend EM Data
- Interpretation of results
- Retrieve important information on the condition of the manufacturing facility
- Trend analysis and review of data

*** Bonus Material**
- Example of FAT and SAT protocols are reviewed

David W. Vincent, M.Sc., CEO, **Validation Technologies, Inc.**

SESSION 12: Critical Cleaning Processes — Eliminate Residue, Rouging and Corrosion

I. Ensure Your Organization has a Comprehensive Cleaning and Disinfection Program
- Review of disinfectant regulations
- Evaluate what elements make cleaning and disinfection successful

II. Standards for a Successful Disinfectant Validation
- Testing required for disinfectant validation

III. Keep the Cleanroom Clean
- Understand important mechanical controls
- Learn SOPs to effectively disinfect the cleanroom

IV. Keep Safety at the Forefront — Ensure Proper Application Techniques of Disinfectants
- Application of disinfectant products in cleanrooms and controlled areas
- Troubleshoot problems related to cleaning and disinfection

Clayton W. Foutch, Vice President of Sales, Life Sciences, **Foamtec International, WWC**

3:00 Networking Refreshment Break

3:30-5:00 Choose Between Four 90-minute Sessions (13-16)

SESSION 13: 21 CFR Part 11 — Computerized Analytical Instrument Validation

I. Team Interaction
- How do they perform validation?
- Overcome major challenges
- Who is responsible and accountable?
- Why 21 CFR part 11 is critical to follow?

II. FDA Regulatory Requirement
- Review the history and clarification of guidance
- Why FDA is focusing on 21 CFR part 11
- Example of FDA inspections and 483 observations
- Define 21 CFR part 11

III. Current Validation Requirements
- Risk assessment & change control
- Validation documentation
- Validation execution
- Roles and responsibilities
- Re-evaluation of validated instrument

IV. Hints and Points to Share
- Alignment between SOP, GAMP and other regulatory policies
- Example of templates
- Example of electronic validation database
- How to decide to upgrade the software and what to consider

Haideh Tehrani, Senior Manager, Quality Control Validation/Stability, **Bayer HealthCare**

SESSION 14: Conduct a Gap Analysis of Your Validation Program

I. Formulate Clear Objectives and Goals
- What are you trying to achieve and why?
- Communicate for success

II. Identify your Future State
- What the regulations say
- How to benchmark validation
- Develop your validation Quality System blueprint
- Understand the organizational maturity model

III. Analyze your Current Situation
- Gap assessment versus audit
- Develop effective communication tools
- Perform a consistent analysis

IV. Bridge the Gap
- Perform gap risk assessments
- Developing a remediation plan
- Effective CAPA Planning

* Bonus Material
- Example of a validation program blueprint

Dawn Tavalsky, Director Validation, **Genzyme, a Sanofi company**

SESSION 15: Statistics in Validation — Sampling Plans that Result in Statistical Confidence

ADVANCED

I. Sampling Plans to Meet Validation Objectives
- Understand and establish performance Levels
- Statistical confidence statements
- Sampling plans to demonstrate required performance level

II. Select Best Sampling Plans
- Variables versus attribute
- Single versus multiple

III. Statistics Throughout Validation Lifecycle
- Design verification
- OQ/PQ sampling plans
- Statistical monitoring — Post PQ

IV. Interactive Exercise
Participants apply techniques covered during this session to demonstrate that a process meets a specified validation performance level.

Jacalyn Schroeder, Quality Engineering Specialist, **3M Company**

SESSION 16: Conduct a Retrospective Validation

MEDICAL DEVICE

This case study examines how one medical device company went about correcting the bad situation of having unvalidated equipment in manufacturing and unvalidated software automating functions within its Quality System. Attendees analyze the full remediation lifecycle, from inventory to evaluation.

I. Introduction to Retrospective Validations
- Why bother?
- Benefits

II. Retrospective Validation Program Steps
- Inventory
- Assessment
- Remediate
  - * techniques for individual retrospective validations
  - * tracking, documenting and reporting results
- Evaluate

III. Interactive Exercise
In this exercise, attendees are presented with a scenario that requires retrospective validation, and are asked to develop a strategy for accomplishing this task.

Joseph Zec, Senior Validation Manager, **Philips Healthcare**

5:00 Close of Day Two

DAY THREE, THURSDAY, OCTOBER 24, 2013

7:30 Continental Breakfast

7:30 EYE-OPENER Breakfast Discussion

Risk and the Risk Mitigation Continuum — The GMP Perspective

I. What Is Risk and How to Quantify It
- Review the definition of risk
- Explore events that can result in increased risk in drug manufacturing
- Understand the factors which determine the level of risk and calculate the RPN

II. FDA's Suggested Quality Systems to Reduce Risk to the Consistent Product Quality
- QbD, PAT and CAPA
- Where within the manufacturing lifecycle lies the highest risk?
- The concept of continuous risk mitigation
- Mitigate risk in the design stage, the process performance qualification stage and the continuous process verification stage

* Bonus Material
- A copy of a peer reviewed article — "The Risk Mitigation Continuum and GMP Compliance"

Gamal Amer, Ph.D., Chemical Engineering Adjunct Professor, **Widener University**; *and Principal,* **Premier Compliance Services, Inc.**

8:30-10:00 Choose Between Four 90-minute Sessions (17-20)

SESSION 17: Validation Master Plan (VMP) Development — A Risk-Based Approach

I. Overview And Regulatory Need
- What is a Validation Master Plan, and why is it important?
- What are the various stakeholder expectations (manufacturers, regulatory authorities)?
- Who is ultimately responsible for a VMP?

II. "Doing Less With More"
- Regulatory compliance philosophy
- Cost-effective planning with fewer resources
- Risk-based approach to achieving success

III. Develop the Document
- Format and content guidelines
- Reviews, approvals, publishing and change management

IV. Get to the End Goal
- The importance of value-added activities
- Avoid activities that drain time and resources
- Gauge plan effectiveness — Measurement and metrics

V. Interactive Exercise
Using an example based on a real life sciences project, participants break up into teams of 4-5 people and develop an outline of a VMP. Groups present their findings and discuss difficulties encountered.

Paul Melamud, EIT, PMP — Validation Manager, **QPharma, Inc.**

SESSION 18: Understand and Handle Variation

PHARMA

I. Understand Variation
- Types of variation
- Measure and calculate variation
- The funnel experiment

II. Statistical Signals and Control Charts
- What are they and how can they help me
- Common statistical trends
- Multivariate trending
- Understand the organizational maturity model

III. Make Changes to Your Process
- Over-controlling the process
- Where to focus your efforts
- Process control activities

*** Bonus Material**
- Relevant Industry articles on understanding and working with process variation

Dawn Tavalsky, Director Validation
Genzyme, a Sanofi company

SESSION 19: Detect and Control Variation

MEDICAL DEVICE

I. Types of Variation
- Common causes
- Special causes

II. Tools for Detecting and Controlling Variation
- Understand variation within manufacturing processes and inspection methods
- Understand run sheets, control charts, and Statistical Process Control (SPC) for detecting and controlling variation
- Determine the sampling plan for detecting and controlling variation

III. Detect and Control Variation
- Establish methods to detect variation
- Implement a process monitoring program for specific processes to detect variation
- Document the data of the process monitoring program and data analysis for reducing variation
- Methods for controlling variation

IV. Interactive Exercise
Using a real life example, participants study how to develop methods to detect and control variation for cleaning processes for invasive wire guides and high-volume manufacturing of needles and syringes.

*** Bonus Material**
- Examples of selected run sheets and control charts

J. Sean Osso, Senior Systems Engineer and Global Process Owner of Validation,
Dako Corporation, an Agilent Technologies Company

SESSION 20: Reduce Waste in Process Validation

I. What Constitutes Process Validation?
- Identify the three stages of process validation
- What are the requirements for a successful process validation?
- What does waste in the process validation exercise look like?

II. What Causes Waste in Process Validation?
- Reasons for waste
- How does waste manifest itself in the various stages of process validation?
- ICH Guidance (ICH Q8, Q9) and reducing waste
- FDA's 2002 initiative on risk based compliance and reducing waste
- Having a robust Quality System for reducing waste

III. Reduce Waste and Achieve Savings in the Three Stages of Process Validation
- Identify CQA and CPP as a way to reduce waste
- Define risk and ensure that highest risk elements are addressed
- Proper identification of acceptance criteria and its importance in reducing waste
- Leverage your supplier's information
- Have the appropriate and complete documents for conducting a successful validation
- Monitor the correct processing parameters

IV. The Ten Steps for Performing Process Validation to Ensure that Waste During the Effort Is Reduced
- A ten step approach process validation that is designed to reduce waste and improve the efficiency of implementing process validation

Gamal Amer, Ph.D., Chemical Engineering Adjunct Professor, **Widener University;** *and Principal,*
Premier Compliance Services, Inc.

10:00 Networking Refreshment Break

10:30-12:00 Choose Between Four 90-minute Sessions (21-24)

SESSION 21: Implement Risk Management in the Validation Process

I. Risk Management 101 — Only The Good Stuff

- Quality Risk Management (QRM) process, principles and philosophy (ICH Q9)
- Quality by Design (QbD) — Employ risk management in product and process design (ICH Q8 and Q11); product and process characterization
- Bring it all together — QRM and QbD in the Quality System (ICH Q10)

II. Use Risk Assessment To Design Your Validation Strategy

- Review commonly used risk assessment tools, pros and cons
- Roles and responsibilities — Who, what, when and why
- Validation for new versus legacy products/processes
- Define validation parameters, number of lots, acceptance criteria, revalidation scope and frequency
- Validation as risk mitigation — Alternative theories of risk

III. Interactive Exercise

Attendees review a completed risk assessment and learn how to develop a validation strategy based on that analysis.

Kelly Waldron, Principal Continuous Process Improvement Analyst,
Genzyme, a Sanofi company

SESSION 22: HVAC and Purified Water System Validation — Case Study

I. Design Phase for HVAC and Purified Water Systems

- Review of example of P&IDs and drawings HVAC and purified water system
- Requirements for conceptual design
- Risk assessment for HVAC and purified water systems

II. Commissioning and Qualification

- URS and other support documents
- Perform a System Impact Assessment (SIA) and Critical Component Analysis (CCA)
- Example of FAT and SAT protocols
- Risk assessment for HVAC and purified water systems
- What information should be included in the IQs, OQ and PQ protocols for HVAC and purified water systems

III. Comparisons between FDA and EU Expectations

- Latest trends
- Controversies regarding sampling times and durations
- 483 and regulatory observations

*** Bonus Material**

- Example of a validation protocol

David W. Vincent, M.Sc., CEO,
Validation Technologies, Inc.

SESSION 23: Establish Testing Criteria for Validation

I. Provide Assurance and Specifications that the Product/ Software Works as Intended

- Validation "V-model"
- User Requirement Specification (URS)

II. How to Develop a Test

- Conduct a risk assessment
- Develop a control strategy to ensure product/software quality

Yau Kai Wong, Associate Director, QA Validation,
Novartis Pharmaceuticals Corp.

SESSION 24: The Establishment of an Effective Requalification Program

I. Establish the Rational

- Develop a site Validation Master Plan
- Track the program
- What makes sense vs. what is required
- FDA and EU similarities/differences
- Identical equipment — When is rotational requalification acceptable?

V. Organization — The Key to Controlling Requalification

- Equipment vs. process vs. utility
- Protocol or procedure
- Why a qualified database is important
- Scheduling activities
- You've executed, now what?
- Deviations and potential impact

VI. The Importance of Critical Change Review (CCR)

- Execute before any testing begins
- How deep do you go?
- Requalification vs. revalidation — How CCR is the trigger
- Change control and validation assessment

VII. Interactive Exercise

After going through an agency audit, changes are required to the chamber requalification program. Participants work through the steps necessary to achieve a timely redesign and schedule adherence plan to satisfy the change while staying within your policies.

*** Bonus Material**

- Example of requalification program procedure

Mark D. Rafnson, Senior Manager, Validation,
Gilead Sciences, Inc.

12:00 Networking Luncheon

1:00-2:30 Choose Between Four 90-minute Sessions (25-28)

SESSION 25: Equipment Qualification — Fit for Intended Use

I. The First Step — Master Validation Plan
- Where and what areas of the company
- Clarify what needs to be validated
- Identify critical equipment
- Legacy versus new equipment
- Define intended use

II. Manufacturing Equipment
- Requirements for qualification
- How do you satisfy intended use?

Justin Roose, Senior Validation Engineer, **Amway**

SESSION 26: Documentation Requirements and Strategy for Each Stage of the Process Validation Lifecycle

I. Definition and Discussion of the Stages of the Process Validation Lifecycle
- Identify activities and tasks included in the lifecycle
- Discuss the function of each deliverable
- Identify which deliverables are a business system or function, and which are part of the Quality System

II. Ordering and Optimization of the Stages of Process Validation
- Identify the documentation method and requirements
- Explore the opportunities presented by the overlap or redundancy of the documents identified
- Consider and integrate change control into the lifecycle at the appropriate time
- Learn importance of swabs selection based on your method

III. Interactive Exercise
Throughout the session, attendees participate in the identification, ordering and optimization of the approach using a generalized pharmaceutical process as reference material. Participants are put into groups to simulate the team dynamic that occurs during process implementation project.

Rod Freeman, PMP; Manager – Validation and Verification Engineering, **Beckman Coulter, Inc.**

SESSION 27: Manage the Validation Quality System

I. Lifecycle Approach to Validation Quality System
- Validation business process
- Multiple types of processes and equipment to be validated
- Validation/qualification initiation responsibility
- Risk management
- Design, performance and review quality system metrics

II. Application to Other Quality Systems
- FDA Quality Systems audit approach
- Stand-alone Quality Systems
- Quality Systems supporting multiple functions

III. Positives and Negatives
- System performance orientation
- Strong message to employees and to auditors, "credit" in audits
- Consistency with FDA direction (process validation, risk), ASTM E2500, and ICH Q8, Q9, Q10
- Cost effectiveness — Highest risk activities emphasized and prioritized
- Implementation challenges, internal audits, transparency, identify deficiencies and make commitments

IV. Interactive Exercise
Attendees discuss the lifecycle approach to Validation Quality System, positives/negatives, impediments to implementation, etc.

Paul L. Pluta, Ph.D., Editor-in-Chief, Journal of Validation Technology and Journal of GXP Compliance, **IVT Network/Advanstar Communications**, *and Associate Professor of Biopharmaceutics,* **University of Illinois at Chicago (UIC) College of Pharmacy**

SESSION 28: Align FDA's Process Validation with ICH Q8, Q9, and Q10

This session addresses the alignment between FDA's Process Validation Guidance and ICH Q8, Q9, and Q10.

I. The Path to The FDA Process Validation Guidance
- 1987 Process Validation Guidance
- Proposed amendments to the GMPs
- Industry input
- FDA inspectional guidance

II. Other Process Validation Guidance
- EU
- WHO

III. Similarities And Differences — An Interactive Discussion
- Discuss how the Process Validation Guidance aligns with other guidance and standards.

IV. What Is Happening/Will Happen — An Interactive Discussion
- FDA actions
- The fate of "three batches for validation"
- The ultimate practice

*** Bonus Materials**
- Copies of the FDA Process Validation Guidance and the EU Process Validation Guidance

Jerry Lanese, Ph.D., President, **The Lanese Group, Inc.**

2:30 Networking Refreshment Break

2:45-4:15 Choose Between Four 90-minute Sessions (29-32)

SESSION 29: Continued Process Verification — Periodic Review of Process Design, Development and Maintenance

I. Maintaining Qualified State of Manufacturing Systems
- Periodic review
- Change control
- Analytical instrument performance verification
- Requalification
- Deviation management
- System monitoring
- Preventative maintenance and calibration
- Alarm management

II. Maintaining the Validated State of Processes
- Process monitoring
- Method validation/revalidation
- Cleaning validation/revalidation

Aaron Chesnut, Senior Validation Manager, Drug Substance Operations, **Allergan**

SESSION 30: Audit Vendors on Validation Practice

I. Ensure All Inherent Systems Used are Validated and Compliant with FDA Rules and Regulations
- Understand the current regulatory environment
- Demonstrate applications are developed, tested and maintained
- Demonstrate the proper use of the procedural and technical controls
- Ensure applicable regulations are met

II. Conduct a Vendor Audit
- Purpose of audit
- Basic components of an audit program
- Audits as an asset
- Establish relationships with vendors and buyers
- Increase product quality
- Reduce duplicated testing efforts
- Develop constructive dialogues

Yau Kai Wong, Associate Director, QA Validation, **Novartis Pharmaceuticals Corp.**

SESSION 31: PQ Forum — Validation Documentation Challenges

III. Objectives
- Discuss frequent PQ documentation problems and proposed solutions
- Identify additional problems

IV. Definitions
- Validation business process
- Validated processes, equipment, utilities, computer systems, others
- Process of validation — Lifecycle approach to process validation
- Validation Quality System
- Quality by Design (QbD)
- Risk management

V. PQ Initiation Problems
- What is being validated, why and how?
- Validation equals confirmation
- Lifecycle approach to validation and qualification
- Validation Approval Committee (VAC) responsibilities
- Amendments

VI. PQ Technical Writing Problems
- Three simple rules

VII. PQ Data Problems
- Sampling pages
- Data pages
- Original data
- Retrieval of original data

VIII. PQ Result Problems
- Deviations
- Project objective — Is it validated?
- Post-validation monitoring based on risk

Paul L. Pluta, Ph.D., Editor-in-Chief, Journal of Validation Technology and Journal of GXP Compliance, **IVT Network/Advanstar Communications,** *and Associate Professor of Biopharmaceutics,* **University of Illinois at Chicago (UIC) College of Pharmacy**

SESSION 32: Sampling and Testing of In-Process Materials and Drug Product — A Risk Based Approach

I. Establish Context — Review of Regulations and Risk Management Principles
- Common sampling strategies
- Review of applicable regulations, standards and guidances
- Review of applicable risk management principles
- How can risk help?

II. Use Risk Assessment to Guide your Sampling and Testing Strategy
- Review commonly used risk assessment tools, pros and cons
- Using HACCP to pinpoint sample locations over the value stream (in process materials)
- Intermediate vs. drug product testing
- Risk control strategies to streamline sampling

III. Interactive Exercise
Attendees develop a generic HACCP risk assessment to define sampling strategy

Kelly Waldron, Principal Continuous Process Improvement Analyst,
Genzyme, a Sanofi company

4:15 Close of Conference

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Wednesday, October 23, 2013

8:30 – 10:00	①	②	③	④
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1:30 – 3:00	⑨	⑩	⑪	⑫
3:30 – 5:00	⑬	⑭	⑮	⑯

Thursday, October 24, 2013

8:30 – 10:00	⑰	⑱	⑲	⑳
10:30 – 12:00	㉑	㉒	㉓	㉔
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profiling (i.e., the relative distribution of carbohydrate structures).

In addition to MS, a host of other analytical techniques should be used to compare the structure of both the biosimilar and originator at primary and higher-order levels. Various chromatographic, spectroscopic, and electrophoretic methods can be used to interrogate and compare on the basis of size, charge, and shape. Co- and post-translational modifications, fragmentation, aggregation, deamidation, and oxidation should all be studied and compared. Techniques such as near and far UV circular dichroism provide information on the folding and secondary and tertiary structure of the protein and can be used in a comparative sense. Depending on the molecule, nonroutine techniques such as protein nuclear magnetic resonance (NMR) and x-ray crystallography may also be used. In fact, a whole panel of methods should be employed, including orthogonal techniques to analyze particular quality attributes. The concept of 'fingerprinting' the molecule has been raised in the FDA guidelines.

It is clear from the new EU guidelines that the primary protein structure (i.e., the amino-acid sequence) must be the same. The guidelines, however, anticipate that minor differences in post-translational forms or product-related impurities may exist and that these products should be investigated with regard to their potential impact on safety and efficacy so that it is the total package of data that will be taken into account on a case-by-case basis. FDA has adopted a similar approach, in that the analytical characterization should show that it is 'highly similar to the reference product notwithstanding minor differences in clinically inactive components.'

Rabia Hidi, PhD, director of biomarkers & biopharmaceutical testing, Laboratory Services, SGS

Hidi (SGS): An initial step of the comparability exercise is the analysis of the primary structure of the molecule. Change in the primary structure of a biotherapeutic compound could affect the downstream higher-order composition, which could have impacts on the clinical activity. Essentially the tridimensional structures (tertiary or quaternary) are very important as they could greatly impact the biological function. Finally, post-transcriptional modifications (e.g., phosphorylation, glycosylation, lipid attachment and/or intentional modifications, such as PEGylation), should be thoroughly characterized as these can affect all forms of higher-order structure and can impact efficacy as well as immunogenicity in the clinic.

Functional assays for testing biological activity can play an important role in filling the gaps in data from higher-order structural qualities. Bioassays should be developed for high precision and sensitivity to detect *in-vitro* functional differences between the biosimilar and the reference compound. These assays should express the relative potency in which the activity of the biosimilar is determined by comparison to the reference compound according to *European Pharmacopoeia* and *US Pharmacopeia* recommendations.

Ideally, bioassays should allow an assessment of all functional domains of a biosimilar candidate during comparison to the originator. An example of multifunctionality is the therapeutic monoclonal antibodies. Conventional assays for testing the functions of Fab and Fc domains of therapeutic antibodies are widely available. These include *in-vitro* target binding (either on intact cells or using soluble target), ADCC, CDC, programmed cell death (PCD) and surface plasmon resonance (SPR) Fc receptor binding assays.

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10. Patient Protection and Affordable Care Act of 2010, Public Law 111-148 (2010).
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WEB For an extended version of this article that includes a discussion on the safety issues that must be considered when developing a biosimilar product, please visit PharmTech.com, or click on the QR code at the right using your smart phone to go directly to the article.

Gauging the outlook of the biologics market

Biologics are among the most expensive pharmacotherapies as noted by IMS Health, and yet, there is a growing demand for these specialty drugs as they continue to outperform in the global market, delivering novel treatment alternatives for a variety of diseases. The biologics market is fuelled by launches of recombinant insulins, human growth hormones, erythropoietins, granulocyte colony stimulating factors, and the monoclonal antibodies, which are reported to have the strongest R&D pipeline. *Pharmaceutical Technology* spoke to Mike Jenkins, general manager of Catalent Biologics development and manufacturing facility in Madison, WI, about the evolving landscape of the biologics market and the development and manufacture of these innovative products.

The full interview is available at: PharmTech.com/biosimilars_MikeJenkins

Best Practices for Restricted Access Barrier Systems

GLOWIMAGES/GETTY IMAGES

PharmTech.com/Troubleshooting

Joerg Zimmermann

RABS maximize product control but minimize operator interaction.

It seems intuitive that the manufacture of pharmaceutical products must be free of all contamination risk. After all, patients must rely on the safety of the final product. Looking back, as early as 1822 a French pharmacist demonstrated that physicians could use solutions that contained chlorides of lime or soda as disinfectants. He concluded independently that the hands of health personnel spread puerperal fever and that sterilization measures could be taken to prevent transmission of pathogens.

Today, almost 200 years later and with approximately 2200 commercial production lines in conventional cleanrooms in operation worldwide (1), we still deal with the introduction of the human element as we seek the highest possible level of sterility and the prevention of cross contamination in aseptic manufacturing. In the highly competitive and global world of parenteral manufacturing, along with ever-growing costs and increasingly stricter regulatory demands, optimized processes to reduce contamination sources are essential.

Since the early 1990s, two systems emerged that have helped the manufacturer assure a higher level of contamination-free product—the isolator and the restricted access barrier system, commonly referred to as RABS. The isolator was the first system developed to help enable a high level of sterility. By definition, the isolator allowed for full isolation of the machinery from the environment. Such units help keep the processing of the product separate from human intervention.

Joerg Zimmermann is director of process development and implementation at Vetter, www.vetter-pharma.com.

Simply installing restricted access barrier hardware in a facility does not create a RABS.

In the earlier phase of its development, technical issues and discussions around validation of sterilization or decontamination of the isolator were a problem. These issues have since been overcome and vast improvements have helped make the isolator a safe and proven process that is used in over 430 commercial lines (1). However, the limitation of the isolator continues to be lengthy changeover time. Thus, isolators are most effective in mono-lines that run the same product continuously, especially products requiring containment such as potent/cytotoxic drugs.

The second manufacturing system developed in the mid-90s was the RABS (see **Figure 1**). Recently, the demand for RABS lines has become more prominent. A primary reason for this development is the enhanced flexibility RABS offers beyond the isolator. RABS can allow for faster start-up time, ease of changeover, and reduced capital costs, particularly with retrofits and renovations. As a result, today there are approximately 250 RABS units in operation worldwide.

What is a RABS?

With the emergence of RABS among contract development and manufacturing organizations, agencies involved in overseeing those manufacturers, such as FDA, demanded that a more precise definition of RABS be put into place to ensure consistency among its users. They believed that simply installing restricted access barrier hardware in the manufacturing facility does not create a RABS. In 2005, FDA commissioned a study group to develop a definition and determine what elements need to be included to ensure that a RABS system is truly in place before a manufacturer can make such a claim. The International Society for Pharmaceutical Engineering (ISPE) study group consisted of experts from major manufacturers including Bosch Packaging Technologies, Pfizer, Merck, GSK, and Vetter, along with members of FDA.

By the definition developed by this ISPE group (2), any system claiming to be a RABS must include quality-designed equipment, and all operators must receive comprehensive training in key practices such as proper gowning practice. Additionally, all RABS must also include the following:

- A barrier to prevent human intervention directly into the critical zone
- Airflow for an ISO 5, at least in the critical zone
- Glove ports and transfer ports used for interventions (see **Figure 2**)
- High-level disinfection
- Highly automated processes and well-defined procedures for rare open-door interventions.

The system goes beyond encasing the production lines from the environment

only. RABS combines the high aseptic safety of an isolator with the flexibility of a conventional cleanroom. The inclusion of rare open-door interventions in the definition often leads to criticism. These interventions, however, are not considered a best practice.

Best practices for RABS

RABS provides a level of separation between the operator and product that affords product protection superior to traditional systems. However, to operate a RABS cleanroom successfully, several best practices must be followed.

No open-door intervention allowed. During operation, the barriers may not be compromised; lifting the separation can lead to contamination and increased risk to the product. Therefore, when aseptic operations are carried out in a RABS, it is the intent to fully eliminate the need to open RABS doors. If the filling is interrupted with an open-door intervention, a complete cleaning and line clearance must be carried out, and the batch is eliminated.

During the line set-up stage, all machine parts and formats must be installed with the barrier closed by using a special glove-portal system. Thorough mock-up studies when designing a machine are essential. Such studies allow a well thought-through configuration of the machine and the barrier around it that allows the operator to reach all areas within the machine using the gloves. The mock-up studies simulate all routine operations and potential interventions on the machine. Operators of different departments (e.g., engineering and quality assurance) join forces to ensure the mock-up studies are as effective as possible.

High-level disinfection. Disinfection after each production batch must be completed. Once the filling process and the monitoring of the microbiological environment have been completed, the barriers are opened for cleaning. This is followed by a high-level disinfection with a sporicidal agent (e.g., peroxide suspension), which generates oxygen radicals to avoid build-up of resistance.

Integrity of gloves. Following production, all gloves must be tested for integrity and sterilized. Using a pressure-decay test, the gloves are removed and tested for even the smallest damage that could compromise the system. If the gloves are found to be airtight, they can be cleaned, steam-sterilized, and remounted back into the glove ports for use in the next production batch.

Figure 1: A commercial restricted barrier access system (RABS).

Figure 2: Glove ports are used for a filling operation.

Aseptic transfer systems for zone transition. Materials and formats are only carried into the ISO 5 area using aseptic transfer systems. Any parts used in the production, including any raw materials such as syringes and stoppers, are sterilized in steam or dry heat and double packed. The outer packaging is sprayed with a sterilizing agent containing alcohol before being transferred to the ISO 5 area through a lock, and the outer packaging is removed. All steps are performed using the glove portal system. Packaging materials are also put into sterilized bags and placed in special containers. The containers are sprayed down prior to introduction so when they are opened inside the barrier, the content is exposed to ISO 5 conditions only.

Conclusion

A RABS process is secure, with both a cleanroom design and aseptic safety comparable to an isolator, but with a higher degree of flexibility. Automation of the system reduces variability due to operators and makes the entire process reproducible. At Vetter's Ravensburg South production facility, for example, approximately 4 million media-fill units were filled over 7 years in 3 different cleanrooms with RABS units with no resulting contaminated units.

The RABS system is a proven and effective approach to favorably impact cleanliness in the finished product. RABS is also one of the most effective and efficient responses to current and future challenges in the manufacturing of aseptic products.

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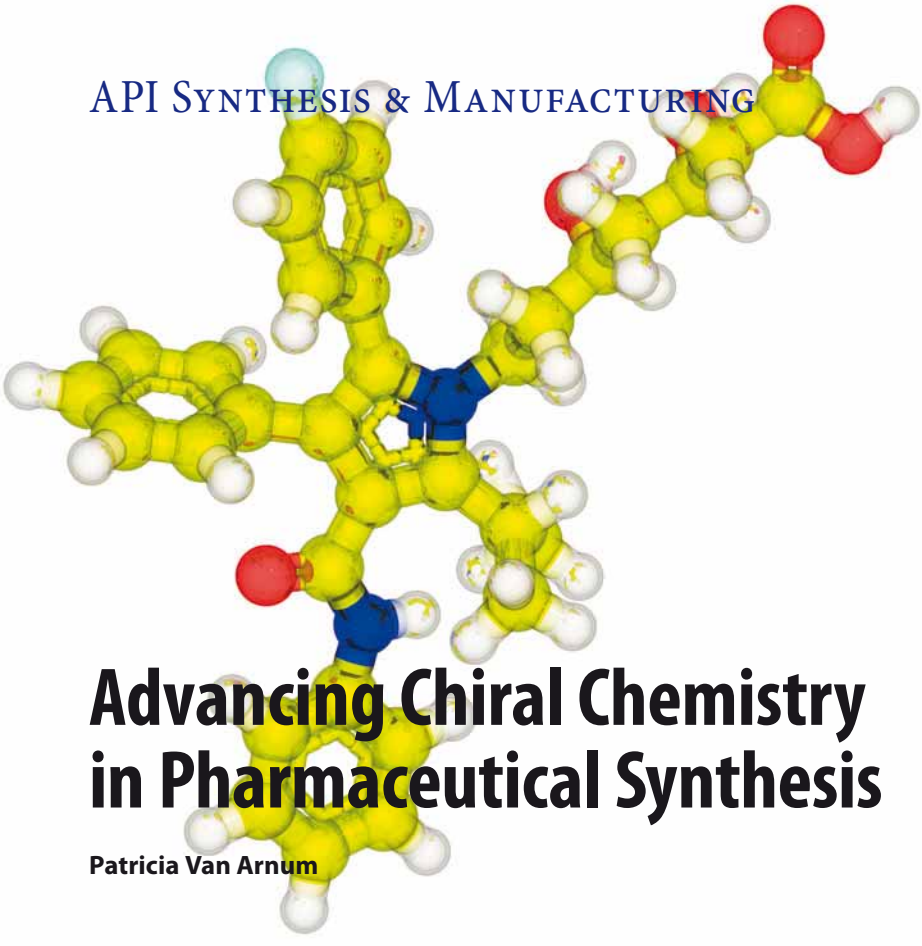

Advancing Chiral Chemistry in Pharmaceutical Synthesis

Patricia Van Arnum

Developments involve stereoretentive cross-coupling, enantioselective alcohol silylation, strategies for amplifying signals in circular dichroism spectroscopy, and a synthetic route for the natural product ingenol.

Chiral chemistry plays an important role in pharmaceutical development and manufacturing. Strategies in asymmetric synthesis to produce single-enantiomer drugs as well as methods for detecting and quantifying chirality are important tools for pharmaceutical chemists. Some recent developments involve stereoretentive cross-coupling for producing libraries of single enantiomers, an approach in enantioselective alcohol silylation, strategies for amplifying signals in circular dichroism spectroscopy, and a synthetic route to the natural product ingenol.

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Stereoretentive cross-coupling

Mark R. Biscoe, assistant professor of chemistry at the City College of New York (CCNY), and his team recently reported on a new method for preparing libraries of single-enantiomer molecules for therapeutic and toxicity studies that is faster and potentially less costly than methods now used in the pharmaceutical industry, according to a Aug. 15, 2013 CCNY press release. Specifically, the researchers developed a general palladium-catalyzed process for the stereoretentive cross-coupling of secondary alkyl azastannatrane nucleophiles with aryl chlorides, bromides, iodides, and triflates (1). The researchers reported that coupling partners with a wide range of electronic characteristics were well tolerated and that the reaction occurred with minimal isomerization of the secondary alkyltin nucleophile (1). The researchers assert that the process constituted the first general method to use secondary alkyltin reagents in cross-coupling reactions (1).

Enantioselective alcohol silylation

Researchers at Boston College (BC) reported on a new computational approach for enantioselective alcohol silylation (2) that reduced the reaction time to less than one hour, down from a period of two to five days, reduced catalyst loading, and produced an overall more efficient reaction, according to a July 2013 BC press release. Based on a computational projection, the researchers used cocatalysts to achieve the reaction improvements in enantioselective silyl protection of alcohols promoted by a combination of chiral and achiral Lewis basic catalysts (2). The researchers used a cocatalyst model involving two Lewis base molecules adding the achiral molecule to an already present chiral molecule. These cocatalysts operated in concert, with the chiral molecule activating an alcohol, and the additional achiral molecule, from commercially available 5-ethylthiotetrazole, activating silicon, according to the BC release. Identifying the influence of ethylthiotetrazole was a key component and provided the researchers the ability to effectively control the interplay between the cocatalysts. Together, the Lewis bases served as a closely related Brønsted base to allow the catalyst to work faster while retaining high enantioselectivity.

"The bottom line is the reaction goes a lot faster," said Marc Snapper, professor of chemistry at BC, in the BC release. "The practical advance is adding the tetrazole, which greatly accelerated the pace of the reaction by doing a much better job activating the silicon reaction partner." The BC researchers suggest that the new conceptualization of the catalyst could lead to the development of new processes that require separate and independently operational Lewis basic cocatalysts, which can overcome the overlapping functions of cocatalysts and eliminate detrimental effects on the production of new molecules with high enantioselectivity (2).

Nanotechnology in discerning chirality

Researchers at the US Department of Energy's Brookhaven National Laboratory (BNL) and Ohio University have developed a simpler way to discern chirality by using gold and silver cubic

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nanoparticles to amplify the difference in the enantiomers to circularly polarised light, according to a June 26, 2013 BNL press release. The researchers showed that nonchiral nanoparticles, specifically gold/silver core/shell nanocubes, can act as plasmonic reporters of chirality for attached molecules by providing two orders of magnitude circular dichroism enhancement in a near-visible region (3).

"Our discovery and methods based on this research could be extremely useful for the characterization of biomolecular interactions with drugs, probing protein folding, and in other applications where stereometric properties are important," said Oleg Gang, a researcher at Brookhaven's Center for Functional Nanomaterials in the BNL release. "We could use this same approach to monitor conformational changes in biomolecules under varying environmental conditions, such as temperature—and also to fabricate nano-objects that exhibit a chiral response to light, which could then be used as new kinds of nanoscale sensors."

The use of nanoparticles to amplify the signal was done to overcome the weak signal when applying circular dichroism spectroscopy in the ultraviolet range for chiral molecules. The researchers were guided by experimental work that showed that coupling certain molecules with metallic nanoparticles would increase their response to light (4) as well as theoretical work that suggested that the plasmonic particles, which induce a collective oscillation of the material's conductive electrons to create stronger absorption of a particular wavelength, could move the signal into the visible spectrum, where it would be easier to measure, according to the BNL release.

The researchers experimented with different shapes and compositions of nanoparticles and found that cubes with a gold center surrounded by a silver shell are not only able to show a chiral optical signal in the near-visible range, but also were effective signal amplifiers. For their test biomolecule, they used synthetic strands of DNA. When DNA was attached to the silver-coated nanocubes, the signal was approximately 100 times stronger than it was for free DNA in the solution, according to the BNL release. The observed amplification of the circular dichroism signal is a consequence of the interaction between the plasmonic particles and the energy absorbing-electrons within the DNA-nanocube complex, according to the BNL release. The researchers note that the work can serve as a platform for ultrasensitive sensing of chiral molecules and their transformations in synthetic, biomedical and pharmaceutical applications.

In another development, researchers at Harvard University, the Center for Free-Electron Laser Science (CFEL), and the Max Planck Institute in Germany reported on enantiomer-specific detection of chiral molecules by microwave spectroscopy (5, 6). The approach sought to overcome limitations in circular dichroism and vibrational circular dichroism spectroscopy, which are commonly used in analysing chiral molecules, but which produce weak signals and require high sample densities (5, 6). The researchers carried out nonlinear resonant phase-sensitive microwave spectroscopy of gas-phase samples in the presence of an adiabatically switched nonresonant orthogonal electric field. They used this technique to map the enantiomer-dependent sign of an electric dipole Rabi frequency onto the phase of emitted microwave radiation (5, 6) and described how this approach can be used for determining the chirality of cold gas-phase molecules. They implemented the approach experimentally to distinguish between the *S* and *R* enantiomers of 1,2-propanediol and their racemic mixture. "We can soon measure mixtures of different compounds and determine the enantiomer ratios of each," said Melanie Schnell, coauthor of the study in a CFEL release. The researchers plan to apply the technique in a broadband spectrometer at CFEL that could measure the enantiomer ratios in mixtures of substances, and longer term, the method opens a way for separating enantiomers (6).

Synthesis of natural products

Natural products are well-established sources for drug candidates but developing synthetic routes to natural products can often pose a problem. Scientists at The Scripps Research Institute (TSRI) recently reported on their work in developing what they characterize as the first efficient chemical synthesis of ingenol, a plant-derived compound with anticancer potential, according to an Aug. 1, 2013 TSRI press release. The work enables the synthesis of various ingenol derivatives and also sets the stage for the commercial production of ingenol mebutate, the API in Picato, a drug to treat actinic keratosis, a common precursor to nonmelanoma skin cancer. Picato was approved by the FDA and the European Medicines Agency in 2012.

Ingenol mebutate, a macrocyclic diterpene ester, is a purified ingenol angelate extracted from the aerial parts of *Euphorbia peplus* plant. The molecule has eight chiral centers and one "nonrestricted" double bond, thus, there is a theoretical possibility of up to 512 stereoisomers (7). The ingenol mebutate is obtained from the dried, milled aerial parts of the plant by extraction followed by a series of purification steps. The final step of the process involves crystallization (7). In late 2011, the drug's manufacturer, the Danish pharmaceutical company LEO Pharma, collaborated with TSRI to develop an efficient way to synthesize ingenol mebutate and ingenol derivatives. The scientists developed a stereocontrolled synthesis of (+)-ingenol in 14 steps from inexpensive (+)-3-carene and used a two-phase design (8). The researchers assert the results validate that two-phase terpene total synthesis is an alternative to isolation or bioengineering for preparing polyoxygenated terpenoids (8).

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Effective and Efficient Weighing of Potent Compounds

George Hartford, Patty Cheung, Karen Whitaker, Roy Helmy, and Joanne Ratcliff

Working safely with potent compounds presents challenges for the pharmaceutical industry because exposure to minute quantities could potentially cause health effects. Typically, an isolator would be the preferred containment technology for working with the most potent (occupational exposure band five [OEB 5]) compounds but it has drawbacks in terms of cost, space, efficiency, and ergonomics. The authors describe the advantages of using an automated powder dispensing system in a ventilated balance enclosure (VBE) for efficient handling and effective containment of potent compounds. A review of the data proves that air and surface contamination is well within the acceptable limits, demonstrating the applicability of the automated powder dispensing unit in a VBE for weighing potent compounds in the pharmaceutical industry.

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In recent years, pharmaceutical companies have increasingly begun to work with potent compounds (i.e., compounds that are very active pharmacologically, with efficacy at sub-milligram doses). These compounds allow patients to take smaller doses and potentially experience fewer side effects. While this property is advantageous for the patient, it presents a greater risk to the health of analytical chemists working with these compounds because exposure to very small quantities has the potential to cause health effects. In some cases, the quantity of potent compound that can lead to health effects can be extremely small, being practically invisible in air or on work surfaces, which makes containment of these compounds in the workplace especially challenging.

The list of potent compounds of interest to the pharmaceutical industry includes hormones, steroids, and many oncology drugs. These compounds have airborne occupational exposure limits (OEL) ≤ 10 µg/m^3 as an eight-hour time-weighted average (1). For handling these compounds in the laboratory, a classification system is used to assign materials into a series of health hazard categories, or occupational exposure bands (OEB), of increasing severity based upon their inherent pharmacological and toxicological properties. This classification system helps companies identify risks associated with handling the compounds and provides guidance on how to manage them (2). While no official industry standard exists around the banding of compounds, companies typically utilize OEB systems with four to six categories (1). Each health hazard category corresponds to a predefined strategy known to provide the necessary degree of exposure control to protect employees and the environment.

To support research and development as well as manufacturing of potent compounds, several contract manufacturers have made significant investments to build facilities to control exposure to potent compounds (3). Merck & Co., like other companies, has been developing potent compounds. Merck's most potent compounds, known as OEB 5 compounds, typically require an isolator for dispensing milligram to gram quantities to maintain airborne levels below 1 µg/m^3 and surface contamination below 10 µg/100 cm^2 (see **Table I**).

User safety at the forefront

Working safely with these potent compounds presents challenges. Employers are required to minimize the exposure risk by following the "hierarchy of controls." Since substitu-

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Table I: Merck & Co.'s occupational exposure bands. HEPA is high-efficiency particulate air, LEV is local exhaust ventilation.

Occupational exposure bands (OEB)	OEB 1	OEB 2	OEB 3	OEB 4	OEB 5
Potency/toxicity	Slightly toxic	Moderately toxic	Toxic	Potent, toxic, potentially genotoxic	Highly potent, highly toxic
Occupational exposure limits (OEL) (μg/m^3)	≥ 1000	≥ 100 < 1000	≥ 10 < 100	≥ 1 < 10	< 1
Handling requirements	Good laboratory/ manufacturing practices (GLP/GMP). LEV may be needed. No special containment.	GLP/GMP. LEV may be needed. No special containment.	Virtually no open handling. Closed systems and/or controlled by LEV, hoods or HEPA-filtered ventilated enclosures designed for personnel protection.	No open handling. Closed systems and/ or controlled by LEV, hoods or HEPA filtered ventilated enclosures designed for personnel protection.	No open handling. High containment required.

Figure 1: Example of an automated powder dispensing unit.

FIGURE 1 IS COURTESY OF THE AUTHORS.

tion is not an option when developing or manufacturing potent drugs, engineering controls are required to be used as the primary control. The preferred containment technology is often an isolator that maintains exposures below applicable limits. Using an isolator for dispensing and weighing small quantities of these compounds, however, presents space, ergonomic, efficiency, and cost challenges for an analytical laboratory. Merck needed a simple solution to allow analytical chemistry researchers to work in a laboratory environment with OEB 5 compounds. The workflow needed to be safe, simple, efficient, and accurate enough to allow precision weighing while maintaining cGMP compliance.

Automated powder weighing

Merck's analytical laboratory originally invested in a semi-automated powder dispensing unit (Mettler Toledo) to address an increasing demand for routine weighing of non-potent compounds. The system, however, subsequently proved to be an effective solution for handling potent compounds as well (see **Figure 1**).

It consisted of an enclosed semiautomated dispensing unit attached to a regular analytical balance. The compound is sealed in a vial with a dosing head attached to the top of the container. The dosing head is inserted into the unit, and the balance doors are closed before dispensing takes place. Dispensing the compound from a sealed container reduces the risk of airborne contamination. Each dosing head contains a radio-frequency-identification (RFID) chip to enable identification and tracking of the compound, providing process security by eliminating the possibility of selecting or dispensing the wrong substance. The dispensing system is able to accurately weigh compounds from 1 mg to 5 g with a 2% variance and dispenses the required amount of material into a container that is securely located on the balance. Once the desired weight has been dispensed, the researcher can remove the container and place another one on the balance for the next weighing step. Alternatively, a 30-position autosampler can be added to automate the change of target container, which enables up to 30 weighing operations to take place without any user intervention. It is also possible to link a solvent dispensing module, which accurately adds the desired weight of solvent into the target container based on the actual amount of solid dispensed to achieve a desired concentration. This method is an even more precise way to prepare analytical solutions. Compared to conventional manual dispensing, the automated process can be as much as 20 times faster.

A key benefit of automated dispensing is that it reduces user exposure by eliminating the handling of the substance with a spatula and minimizing the risk of spillage. It also reduces the manual actions required by the user, by

Table II: Containment verification data: Air sampling results. VBE is ventilated balance enclosure, < is less than the laboratory limit of detection.

Iteration 1–6 sample numbers	Sample location	Results in micrograms per cubic meter of air (µg/m³)
02S, 07S, 12S, 17S, 22S, 27S	Personal breathing zone samples	< 0.0025 – < 0.0030
03S, 08S, 13S, 18S, 23S, 28S	Left side of VBE face 200 mm from opening	< 0.0025 – < 0.0030
04S, 09S, 14S, 19S, 24S, 29S	Right side of VBE face 200 mm from opening	< 0.0025 – < 0.0030
05S, 10S, 15S, 20S, 25S, 30S	1.8 m from VBE face at height 1.5 m	< 0.0025 – < 0.0030
06S, 11S, 16S, 20S, 26S, 31S	VBE exhaust 200 mm from outlet	< 0.0025 – < 0.0031

Table III: Containment verification data: Surface sampling results. VBE is ventilated balance enclosure.

Iteration 1–6 sample numbers	Sample location	Results in micrograms per 100 centimeters square on the surface (µg/100 cm²)
05S, 09S, 13S, 17S, 21S, 25S	Floor below VBE face opening (right)	< 0.01
06S, 10S, 14S, 18S, 22S, 25S	Floor below VBE face opening (left)	< 0.01
07S, 11S, 15S, 19S, 23S	Horizontal airfoil (left)	< 0.01
26S		0.028
I08S, 12S, 16S, 20S, 24S, 27S	Horizontal airfoil (right)	< 0.01

eliminating the need for repeated opening of the balance door and transferring the compound from the main container to the secondary container to achieve the desired weight.

The automated dispensing system was situated within a high-efficiency particulate air (HEPA)-filtered ventilated balance enclosure (VBE) (Pharmaceutical Containment Technologies [PCT]). The VBE has features key to effective containment such as rounded airfoils around the entire face, a waste chute to minimize researcher movement in and out of the face, safe-change HEPA filtration, and a flow alarm to ensure the face velocity does not drop below 60 fpm (0.3 m/s). The laboratory initially used this equipment to weigh less potent, OEB 3 and OEB 4 compounds, a task that the device performed remarkably well. A question was raised as to whether the capability of the unit could be expanded to handle the safe and efficient dispensing of OEB 5 compounds. After several discussions between Merck Global Safety and the Environment and Mettler Toledo, an experimental evaluation plan was created to assess the ability of the system to reduce airborne and particulate surface contamination during weighing of OEB 5 compounds. As part of the evaluation, OEB 5 materials were provided to the analytical laboratory in containers compatible with the dosing heads as historical air and surface contamination data indicated manual subdivision by analytical chemists in a VBE would not maintain airborne and surface contamination levels below applicable limits for some OEB 5 compounds.

Surrogate control performance evaluation

Verification sampling was performed to validate the equipment containment. Personal protective equipment (PPE) worn during the sampling included safety glasses, a disposable laboratory coat, disposable sleeves, and double nitrile gloves. Air and surface samples were collected during the dispensing of 2 g of naproxen sodium, and subsequent cleaning and PPE removal. Naproxen sodium, a nonsteroidal anti-inflammatory drug, was used because it is recognized by the International Society of Pharmaceutical Engineers (ISPE) as a rigorous challenge agent and a suitable surrogate for assessing containment of potent compounds (4). The sampling protocol included cleaning of the VBE, containers, balance, and the removal of outer gloves and sleeves within the VBE given that proper technique during these activities is crucial to containment and the prevention of surface contamination. Six iterations of the dispensing task were performed, and air and surface samples were collected during each iteration to demonstrate that the controls and the procedures used by the researchers did, in fact, protect them.

In total, six personal air samples and 24 area air samples were collected. All samples collected were below the laboratory limit of detection and well below OELs for the OEB 5 compounds currently being handled in the laboratory (see **Table II**). Additionally, all wipe samples were below the surface contamination limits (see **Table III**).

Conclusion

A review of the air and surface contamination data showed that exposures are low, generally nondetectable. It was concluded that researchers can safely utilize the automated dispensing system to dispense up to 2 g of OEB 5 compounds with OELs > 3 ng/m³, provided that the VBE is properly sited in the laboratory and use of the system is coupled with appro-

contin. on page 56

Overcoming Limitations of Vaporized Hydrogen Peroxide

Hydrogen peroxide is highly potent and highly problematic.

James P. Agalloco and James E. Akers

The use of hydrogen peroxide (H_2O_2) in the global healthcare industry and other industries that require high levels of contamination control has grown steadily. This growth is attributable to the chemical's ability to kill spores and sterilize materials, which has been demonstrated in a variety of practical applications. Properly used, H_2O_2 is an effective sterilant capable of efficient and rapid elimination of contaminating microbes. Some difficulties have been associated with the implementation of H_2O_2 processes in the healthcare field although these issues appear to have been avoided in commercially sterile food and beverage manufacture. Specifically, persistent problems regarding the development of H_2O_2 processes and their subsequent validation have been reported. The author discusses the technical issues associated with achieving lethal concentrations of H_2O_2 delivered in vaporous form on decontamination targets, explores the core scientific principles behind H_2O_2's use in decontamination and sterilization, and provides experience-based solutions to frequently encountered operational issues.

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Hydrogen peroxide (H_2O_2) is an extremely powerful oxidant that is capable of effectively killing resistant spore-forming bacteria over a wide range of concentrations; at concentrations of 3% or less, it is suitable for use as a topical antiseptic (1). H_2O_2 has been accepted by both FDA and the US Environmental Protection Agency (EPA) as a sterilizing agent for many years (2, 3). In the food industry, H_2O_2 is widely used to sterilize containers, closures, and aseptic chambers (i.e., isolators) used for manufacturing low-acid and dairy-based beverages as well as other applications (4).

The potency of H_2O_2 as a sterilant and its usefulness in a broad range of antimicrobial applications are beyond dispute. The problems associated with vaporized H_2O_2 processes in the healthcare industry lie in fundamental misunderstandings concerning physicochemical characteristics of H_2O_2 sterilization. These errors profoundly influence real-world H_2O_2 applications.

Understanding vapors

To fully understand the physical factors that affect the distribution of H_2O_2 in the vapor phase, one must consider the factors that affect vapors in general and the factors that allow them to exist in air, which is the medium in which H_2O_2 in the vapor phase is distributed within a decontamination target. Air contains varying, but small, amounts of water in the vapor phase, which is described using the term relative humidity (RH). An important factor in the distribution of a chemical is the dew point. The dew point is, in simplest terms, a function of both concentration and temperature. When the concentration of water exceeds the saturation point at a particular temperature, condensation occurs. The gaseous water converts to the liquid phase, and droplets of liquid water may appear. On the other hand, if the water concentration is below the saturation point, it will remain in the gas phase. When the temperature of the air is actively lowered (or simply drops as a function of thermodynamics) below the dew point, some portion of the water (H_2O) present as a gas mixed with air condenses and forms liquid droplets. We observe this as clouds, dew, fog, or frost.

The typical H_2O_2 process

The process that most H_2O_2 generator and isolator manufacturers use for H_2O_2 introduction is one in which a hot air stream is used to introduce a heated H_2O_2/H_2O gas into the target environment, which may be an aseptic chamber or isolator. Within the generator, the temperature of the air/H_2O_2/H_2O mixture is sufficiently high that all three materials are in a gaseous state. The hot air is conventionally at temperatures in excess of 100 °C, which takes advantage of the respective boiling points of the pure components (i.e., H_2O = 100 °C, H_2O_2 = 150.2 °C, and a 30–35% aqueous solution of H_2O_2 = approximately 108 °C). At these temperatures, both H_2O_2 and H_2O are present as gases and are carried into the target vessel with the hot air. The H_2O_2/H_2O is supplied as an aqueous solution of H_2O_2 in varying percentages typically ranging from 31% to 50% H_2O_2. At typical room temperatures, each of these solutions is predominantly liquid, and the headspace air within the closed containers has a small amount of gas phase H_2O_2/H_2O that is in equilibrium with the liquid.

If the concentration remains below the saturation point upon introduction into the target environment, then both the H_2O_2 and H_2O will remain in the gas phase. When the hot and relatively humid gas mixture from a H_2O_2 generator is introduced to the target chamber, it will encounter colder air as well as ambient temperature surfaces of the chamber and materials inside it. As the hot gas mixture cools to the temperature of the chamber, it will fall below the dew-point temperature of both H_2O_2/H_2O, and some portion of these materials will condense on the surfaces as liquids. In effect, the H_2O_2/H_2O are returning to their initial equilibrium state of liquids in equilibrium with the adjacent gas, which they possessed before being converted to a gas in the generator.

Condensation that forms on the surfaces will tend to be nonuniform in concentration across the chamber for several reasons:

- The H_2O_2 will condense first due to its lower equilibrium vapor pressure (i.e., lower dew point) relative to H_2O.
- The temperature in the system may be non-uniform across the chamber and is generally hottest near the inlet where the hot gas mixture is introduced; for the purposes of vapor-phase hydrogen peroxide (VPHP) technology, ± 2.5 °C can be considered effectively uniform.
- The continued introduction of the hot gas mixture into the chamber, in which VPHP generators rely on continuous replenishment of mixture vapor, results in a slow increase in temperature within the chamber. This effect is more pronounced in smaller enclosures and those with relatively low mass.
- In larger enclosures, the amount of heat added by the hot air stream laden with H_2O_2/H_2O will have little impact on temperatures remote from the injection port.
- Where the localized temperature within the enclosure is low enough and concentrations of H_2O_2 and H_2O are high enough, they will condense. Many present-day H_2O_2 generator systems are designed such that the process relies on the presence of condensation. In these cases, one should recognize that the heated gas or vapor is used only as a convenient delivery system for the H_2O_2/H_2O to the target environment. The sterilization or decontamination is accomplished by H_2O_2 in the form of liquid condensate on surfaces.
- Depending upon the decontamination approach used, H_2O_2/H_2O introduction during the process dwell period can be continuous, intermittent, or absent entirely. In cases where the hot air/vapor stream is present only during a comparatively short initial introduction period, the effects of the hot air stream on target chamber temperatures will be less profound.
- Chambers with a large number of objects to be decontaminated have added surfaces upon which condensate may accumulate. As the load size increases, the amount of H_2O_2 added and/or the process dwell period may need to be increased to ensure condensation on all target surfaces.

The extent of condensation that occurs depends upon the temperature (i.e., colder locations will have more condensation), the concentration or amount of H_2O_2/H_2O introduced (and removed if a circulating process is used), the size of the enclosure (i.e., affects the surface/volume ratio), and the quantity of material within the chamber (i.e., adds to the surface area).

Phase states in the enclosure

In must be understood that the enclosure will contain a mixture of air/H_2O_2/H_2O internally, with some of the H_2O_2/H_2O in a liquid state on surfaces and the remainder in the gas phase. There is no simple means to establish how much H_2O_2/H_2O is in each phase or where in the chamber a particular phase is present. Additionally one cannot know the percentage of H_2O_2 or H_2O at any single location, and certainly not at every location within the enclosure. The Gibbs Phase rule makes it clear that conditions can vary across the system (see **Equation 1**).

$$F = C - P + 2 = 3 - 2 + 2 = 3 \quad \text{(Eq. 1)}$$

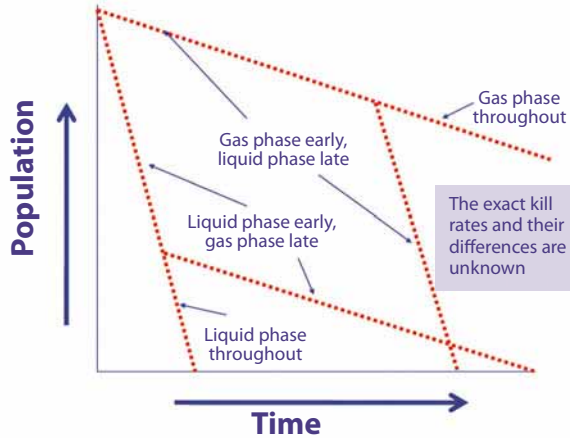
where F = number of degrees of freedom (i.e., concentration, temperature, pressure), C = number of components in the system, and P = number of phases in the system.

Almost nothing is known with certainty with respect to concentration and location. There is, however, one constant in the process: H_2O_2 is lethal to microorganisms in both the gas and liquid phases. It is reasonable to assume that liquid-phase kill will be somewhat faster than the gas-phase kill for two important reasons as further outlined:

- The concentration of H_2O_2 in the liquid phase will always be higher. A 35% H_2O_2 mixture will have equilibrium concentrations of H_2O_2 of ~2% in the gas phase and ~79% in the liquid phase (5).
- The presence of adequate moisture at the point of sterilization is certain in liquids, as H_2O is the other component of the liquid phase.

An older reference describes more rapid kill occurring with H_2O_2 in a gas-phase process compared to a liquid-phase

Figure 1: Estimated relative kill rates in liquid and gas phases; the exact kill rates and their differences are unknown.



process (6). This reference identifies a gas-phase process at 25 °C, with no mention of any liquid H_2O_2 present. At that temperature, however, H_2O_2 is a liquid, so there must be some liquid H_2O_2 in equilibrium with the gas. There is no means to establish that the kill in this "gas" process was actually accomplished in that phase. It is more likely that the cited kill was accomplished in the liquid phase. Misinterpreting what is actually "vapor" as a "gas" has led to the erroneous belief that gaseous-phase kill is more rapid than liquid-phase kill.

The expected microbial kill rates in the system might appear as shown in **Figure 1**, which visualizes H_2O_2 sterilization as a process that occurs within a band, bounded by the extremes of liquid and gas-phase kill. **Figure 1** represents what is believed to occur and does not reflect any specific H_2O_2 process. The absolute slopes of the death curves are unknown. Given that the localized concentrations in both phases are variable due to temperature differences and proximity to the inlet with its heated air supply, it must be recognized that there will be different kill rates in different locations in both the liquid and gas phases. **Figure 1** represents what might occur at a single point within the chamber; similar appearing death curves with differing slopes can be considered for other locations where the local conditions are different. These variations are the underlying cause of the variable performance experienced when using vapor-phase H_2O_2 as a lethal process.

D-values for H_2O_2 decontamination

The death curves in **Figure 1** seem to show that a D-value (or an approximation of one) could be established against a challenge microorganism for the combined processes. That assumption is faulty because there is no way of establishing what conditions (e.g., phase, concentration, or humidity) are present in the system at the point where the microorganism is killed. D-value determination requires knowledge of the specific lethal conditions to which a microorganism is exposed. In a single-phase sterilization process, gas or liquid, information on concentration of the agent, humidity (assumed at 100% for liquid processes), and temperature is readily determined. In the context of H_2O_2, this is easiest for liquids, and published D-values for *Geobacillus stearothermophilus* in various H_2O_2/H_2O liquid solutions are available (1). These liquid phase D-values demonstrate extremely rapid kill (in seconds) at even modest H_2O_2 concentrations (7). At the estimated concentrations where condensation first occurs in vapor H_2O_2 processes, the D-values should be lower as the concentration will be substantially higher than that published in the literature. Unfortunately, no comparable data are available on H_2O_2, where a strictly gas-phase process is present. Thus, any labeled "D-values" for vapor H_2O_2 biological indicators must be considered nothing more than an approximation as the killing conditions are unknown. The conditions of kill may be consistent enough that they could be replicated in an independent study in the same test system. What cannot be established from these labeled "D-values" is how that same biological indicator will respond in a different environment where the conditions are also unknown and most likely substantially different.

In the 20-plus years that this industry has been using H_2O_2 decontamination, a BIER (biological indicator evaluation resistometer) vessel for H_2O_2 has not been developed as a standard for compendial or routine use. The same conundrum faced with respect to variable and unknown biphasic conditions in a larger system has prevented the development of a H_2O_2 BIER. The absence of a BIER vessel and, thus, a fully useable "D-value" for H_2O_2 biological indicators has caused some difficulties. What can be established from the vendor "D-value" is the relative resistance of one lot to another from the same vendor. How any individual lot will perform under different conditions is something the user must determine for each application.

One suggested approach to get beyond this lack of a definitive D-value for a biological indicator is to establish a process or system "D-value" for a biological indicator within a large enclosure and rely upon that as the basis for destruction in the system rather than the vendor's reported value. This approach presumes that the conditions used to establish the process/system "D-value" are representative of the entire system. That assumption is decidedly not the case, nor is it known whether the location(s) chosen for the process "D-value" determination are best case or worst case with respect to kill across the chamber. A number, which is not a D-value in the strict sense, can be calculated, but the utility of that number in any estimation kill rate across the chamber is essentially nil.

Reports of vapor-phase "D-value" variations as a consequence of different substrates must also be recognized as uncertain (8, 9). Because there is no objective biological indicator evaluation method available, published "D-values" are not standardized and thus of very limited use. Unless the concentration on the individual surfaces

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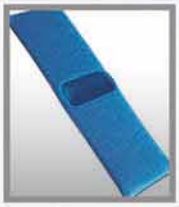

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tested can be known and demonstrated to be constant, any hint that the substrate variations are meaningful must be viewed with some skepticism. There is also some published evidence that "D-values" may vary with spore concentration applied to the carrier material, which means kill may not be linear with concentration. That represents a serious flaw in the use of any biological indicator.

Is safety a concern with H_2O_2?

Given the rapid kill observed in the H_2O_2 liquid phase, the difficulties in attaining consistent kill with H_2O_2 vapor processes can only be explained by a lack of adequate condensation, for there is little doubt then when condensation does occur, kill will be quite rapid (10). Many of the newer generator designs, either freestanding or integrated into enclosures, rely on condensation to decontaminate/sterilize extremely rapidly.

Since the rapid kill provided by liquid H_2O_2 is well documented, why has industry been cautioned to avoid condensation in vapor H_2O_2 processes? The answer lies in the early teachings of AMSCO (now Steris) when the first H_2O_2 generator was introduced in the late 1980s. Caution was routinely raised regarding the potential hazards of high concentrations of liquid H_2O_2. (The H_2O_2 concentration in the gas phase at ambient temperature will always be substantially lower than its equilibrium concentration in the liquid phase.) The relevant safety issues with the use of H_2O_2 vapors are:

- *Explosive vapors.* The caution here relates to concentrations of > 70% H_2O_2 giving off explosive vapors at temperatures greater than 70 °C (11). If this situation were to occur anywhere in vapor processes, the generators themselves would represent the greatest risk. Temperatures inside enclosures rarely exceed 30 °C, and thus the likelihood of this presenting a real-world problem during a sterilization process is unlikely.
- *Hazardous reactions.* There are reports of H_2O_2 reacting with greases, alcohols, ketones, carboxylic acids (particularly acetic acid), amines, and phosphorus. Small amounts of other materials that contain catalysts (e.g., silver, lead, copper, chromium, mercury, and iron oxide rust) can cause rapid decomposition and an explosive pressure rupture of the containing vessel if it is not properly vented (12). None of these compounds and materials is typically present in pharmaceutical enclosures.
- *Corrosivity.* This is possible with some materials, but the typical stainless steel, glass, and other materials exposed to H_2O_2 are known to be compatible and are chosen explicitly for that purpose. The chemical compatibility of H_2O_2/H_2O solutions is well documented.
- *Worker safety.* The US Occupational Safety and Health Administration has established an 8-hour, time-weighted average for exposure to H_2O_2 of 1 ppm, with an immediate hazard in the presence of concentrations greater than 75 ppm (13, 14). This limit is managed in pharmaceutical facilities through external alarms in the surrounding areas and requirements for aeration before personnel or material exposure.

While there is a need for caution with respect to the use of vapor phase H_2O_2, undue concern is unwarranted. In more than 20 years of use in the global industry, there have been no reported incidents of personal injury or equipment damage associated with this process.

Claims that vapor-phase H_2O_2 processes do not result in condensation are speculative. The laws of physics and temperature within enclosures are such that some measure of condensation will always occur, and in many recent equipment and process designs the creation of condensation is intentional. Thus, within the context of real-world experience, the safety issues associated with vapor H_2O_2 systems where condensation is present appear to be adequately managed, assuming appropriate worker-safety precautions are maintained.

Limitations of multipoint process-control measurements

FDA's *Guideline on Sterile Drug Products Produced by Aseptic Processing* recommends: "The uniform distribution of a defined concentration of decontaminating agent should also be evaluated as part of these studies" (15). This suggestion is made without reference to a specific methodology that could be employed. There is no technology that could address this expectation throughout a two-phase environment. Nor would the resulting data on concentration in the gas phase be useful in correlating to microbial kill on surfaces. When appropriate amounts of H_2O_2 are used for decontamination or sterilization, some of the available instruments, such as those that rely on near-infrared transmission, are unusable due to condensation on the lenses. Because accurate measurement is not possible, chemical indicators provide the only widely available means to confirm that H_2O_2 is, or was, present at a specific location.

Problems in an unsteady-state process

The introduction of H_2O_2 into a room-temperature enclosure uses vapor-process heating to convert the liquid solution into a gas for mixing and distribution in hot air. The temperatures in vaporizers are in the range of 105–150 °C. This high temperature results in some localized heating of the enclosure, primarily in locations close to the entry point of the heated materials. The effects of this heat input are multiple:

- Temperatures during the process will change over its duration with the greatest impact found in locations nearest the infeed locations. This heating is more pronounced in smaller, flexible-wall and lightly loaded enclosures where there is less overall mass.
- The resulting changes in temperature will result in varying amounts of condensation (and thus kill) across the enclosure (and also varying over the duration of the process dwell period at a single location).

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- The conditions close to the infeed are more likely to remain in the gas phase throughout the process, which can result in less condensation (if any) and potentially slower kill rates in those locales. In one project, the authors observed that a biological indicator location directly beneath the supply port was repeatedly found to be the only location where the biological indicator could not be killed.

These phenomena are more problematic in those generators where H_2O_2 is fed and removed throughout the process. Systems that operate in a fill-and-soak mode may attain equilibrium conditions within the targeted volume.

The negative consequences of the unsteady-state nature of vapor-phase H_2O_2 processes are unavoidable in recirculating systems. The only means to establish a consistent process is to use enough H_2O_2 that even the warmest locations attain some measure of condensation. This solution is more easily accomplished in the non-circulating systems.

Penetration and adsorption by H_2O_2

Years of experience with vapor-phase H_2O_2 processes have shown how best to address the adverse impact of its adsorption as further explained:

- H_2O_2 can penetrate high-density polyethylene fiber materials (Tyvek, Dupont), which are primary packaging for many presterilized items. Tyvek-wrapped materials of larger dimension may prove difficult to aerate because there is no internal turbulence to aid in aeration.
- Some polymeric materials will adsorb H_2O_2 readily and desorb it very slowly. A small (1 ft^3), empty isolator manufactured from polycarbonate (Lexan, SABIC Innovative Plastics) was found to require more than 24 h of aeration (16). Careful attention to materials of construction is important to reduce any unintended adsorption.
- Typical sterile-product container materials (e.g., glass vial, elastomeric closure, aluminum crimp) and many polymeric materials are largely impervious to H_2O_2.
- Shorter cycle dwell times allowing less overall time for adsorption are generally preferable.
- Aeration periods can ordinarily be improved by additional air changes.
- Liquid H_2O_2 penetration through Tyvek has not been documented.
- Some biological materials have demonstrated extreme sensitivity to H_2O_2 requiring aeration to levels in the parts-per-billion range (17).

The adverse consequences of decontamination and sterilization processes should be considered in the development and control of every process. Vapor-phase H_2O_2 processes, because of their dual-phase nature, present new challenges. Were other gases to be used, similar, but different, concerns would present themselves and appropriate solutions would be identified. A more penetrating agent would only increase the penetration/aeration difficulties encountered, so while H_2O_2 penetration/absorption/desorption is a problem, the situation might be worse with alternative materials.

Biological indicator issues

Difficulties encountered in the destruction of biological indicators have been commonly reported and are so well known that there are some who doubt the efficacy of H_2O_2 as a sterilant. These problems are multifaceted but resolvable when the sterilization process is properly established.

First, H_2O_2 decontamination and sterilization must be understood as a two-phase system. Considering it as a single, gas-phase process has caused more difficulties than anything else. The variability demonstrated in lethality is the direct result of applying process constraints that are suitable for a gas process but inadequate for two-phase H_2O_2 processes. Adapting process models and approaches from the most common gas sterilant, ethylene oxide (EO), to a vapor process created much of the problem. The largest flaw in this thinking is the deliberate avoidance of condensation in endeavoring to make what must be a two-phase vapor process into one that operates in a single phase. Some wrong assumptions are:

- Process conditions (e.g., temperature, relative humidity, and H_2O_2 concentration) throughout the enclosure can be made uniform.
- Condensation is to be avoided at all times.
- Comparatively gentle mixing of the enclosure is adequate.
- D-values for challenge microorganisms can be established.

In the actual two-phase H_2O_2 process, none of these assumptions is correct or attainable at the present time. These assumptions led to the establishment of vapor processes that are inadequate for their intended purpose. They do not adequately induce condensation or use sufficient mixing and thus fail to deliver reasonably consistent conditions throughout the enclosure. The experienced difficulties are a consequence of poor cycle design and not problems with the lethality of H_2O_2.

Second, biological indicators must be specifically designed for the intended process. While there have been attempts at this design, what has been accomplished is largely empirical. The methods used for manufacturing H_2O_2 biological indicators may be identical to those used for other sterilization processes, but because correlation to actual process resistance is lacking, the process suggestions inferred from labeled resistance values are essentially unusable. In the absence of a BIER (and thus truly reproducible biological indicator resistance), the typical biological indicator process response can not be expected for vapor-phase H_2O_2 processes.

The most important attribute of any biological indicator is its reproducible resistance to the intended process. There is no established D-value method, which severely limits the certainty of process understanding and biological-indicator design and selection. Variable results with biological indicators could be attributable to either variations in the biological-indicator resistance or variation in the conditions resulting from poorly conceived controls for a complex process. Lacking a biological indicator whose response to the process is precise, vapor-phase decontamination and sterilization becomes a more challenging process to control.

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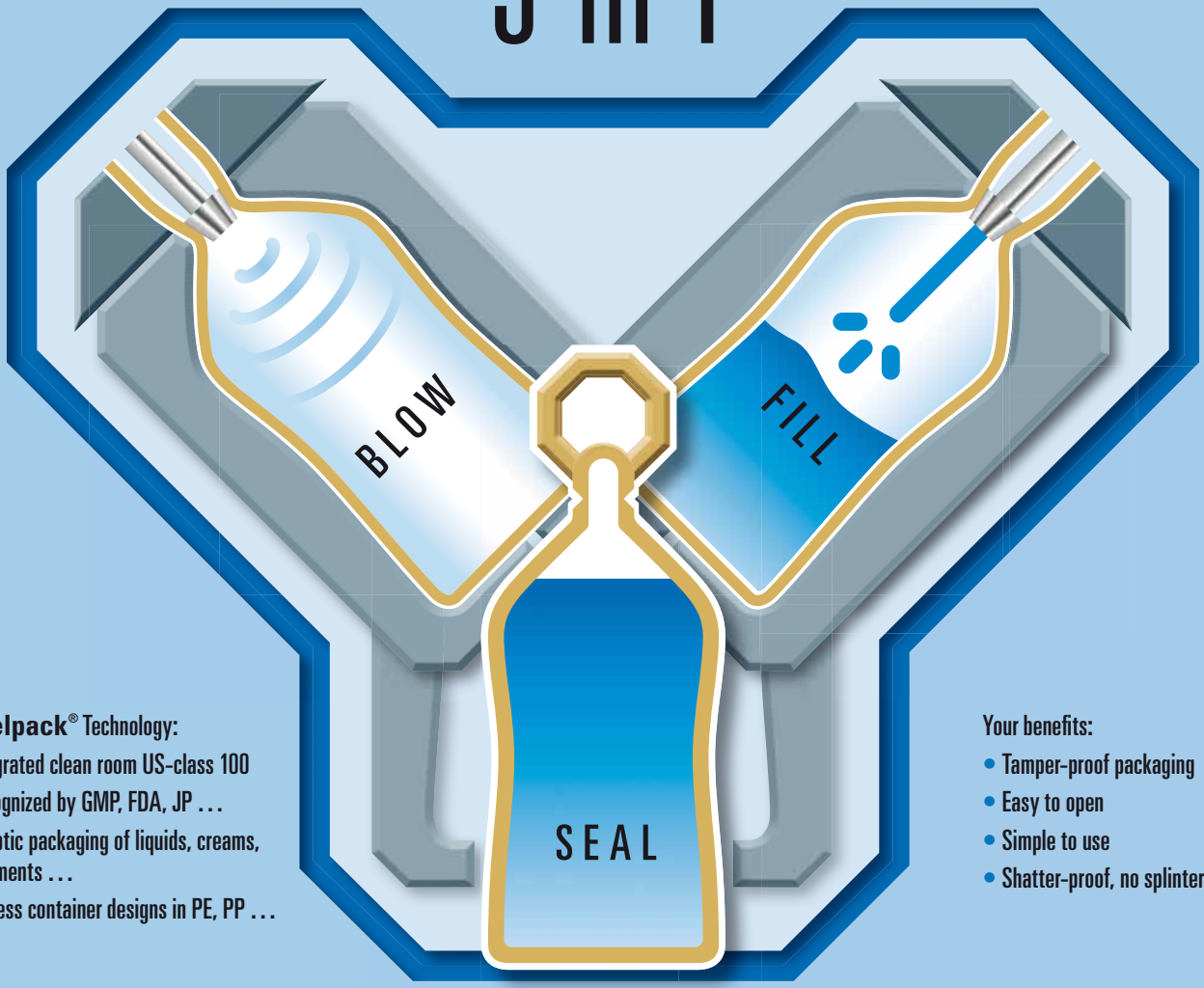

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Third, there is a demonstrated biological indicator concentration effect associated with the H_2O_2 processes unlike that seen in other sterilization processes. Biological indicators with a higher initial population have proven more difficult to kill with H_2O_2 than would be expected based upon the results of the same lot at a lower concentration (18). This phenomenon contradicts the core principle in all sterilization processes that microorganisms die at a constant logarithmic rate regardless of population. Occurrence of this phenomenon in H_2O_2 processes can be attributed to several possible causes:

- Excess cellular debris and perhaps both organic and inorganic salts provide a protective layer of spores. This problem is somewhat exacerbated by the use of stainless-steel coupons that allow these materials to remain on the surface adjacent to the spores.
- The use of biological-indicator populations above what is necessary for process certainty creates potential for clumping of spores through which H_2O_2 penetration may not readily occur. FDA, US Pharmacopeia, EMA, and the Parenteral Drug Association all accept biological indicator log reductions of 4-6 logs, where surface sterilization is not the objective (15, 19-21).
- Some users adhere to an incorrect belief that a 10^6 spore population of the resistant biological indicator must be used to demonstrate a probability of nonsterile unit (PNSU) of $1x10^{-6}$.
- Inadequate processes that rely more on gas-phase kill than the substantially more lethal liquid-phase kill only serve to exacerbate all of the above problems.

All of these are correctable. Using a lower population biological indicator eliminates the first two of these difficulties. A hundred-fold reduction in spore population reduces the amount of debris present at the edge of the biological indicator drop and eliminates spore clumping significantly. This single change would result in more linear death curves than what has been evidenced. The third difficulty is a common mistake that is all too prevalent in the healthcare industry and has no basis in fact (22). The food industry has used H_2O_2 successfully for sterilization for many years and operates without this artificial and erroneous expectation. The last issue is an artifact of the limited process understanding still prevalent on many existing H_2O_2 processes. In cases for which condensation is actively promoted in the process, fewer problems with sterilization are encountered.

Much has been made recently of so-called "rogue" biological indicators. These rogues (i.e., outliers) are presumably biological indicators that failed to conform to the user's expectations of their demise. There is little doubt that the production of spore crops, substrate selection, and the manufacture of biological indicators could result in clumping and encapsulation in contaminants that could result in a lack of uniform performance (23). Properly manufactured biological indicators should be largely free of outliers. Greater frequency of outliers detected in vapor H_2O_2 processes seems to be the result of poor understanding of vapor-phase H_2O_2 that results in marginally lethal processes and the creation of biofilms and clumps of spores on stainless steel at 10^6 concentrations, which result in what are effectively false-positive biological indicators that do not represent the elimination of normal flora at more diffuse concentrations.

Summary and recommendations

The successful use of any decontamination or sterilization process requires a thorough understanding of the underlying principles of the process with particular attention to those aspects that differentiate it from other methods because these represent potential new learning. The two-phase nature of the vapor-phase H_2O_2 process introduces complexities that, if not well understood, can prevent successful use. The healthcare industry has experienced considerable difficulty in the implementation of this process.

The greatest improvements in operating these processes can be obtained through the use of conditions that force some measure of condensation and by recognition that the desired log reduction of these processes need not be excessive given the end use of the enclosure. Only product contact parts must be sterilized, and shifting attention to those locales within the enclosure alone would result in substantial improvements in process outcomes.

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EVENT OVERVIEW:

Organic impurities cover a wide spectrum of compounds that have varying structures, behaviors, and characteristics. Organic impurities can result from manufacturing, storage conditions, or degradation resulting from light, heat, and other external factors. Deciding what technology or analytical methods to use to detect and measure organic impurities is a challenge. This 60-minute webcast will provide insight on regulatory, compendial, and ICH requirements on organic impurity control and analysis. Learn from leading experts on best practices in analytical method development, method selection, and method validation for detecting and quantifying organic impurities in drug substances and drug products.

Key Learning Objectives:

- Learn from experts on the latest regulatory and compendial requirements for organic impurity control and analysis in drug substances and drug products
- Gain insight on selecting the appropriate analytical methods for detection, analysis, and quantification of organic impurities
- Learn from case studies on how best to ensure product quality

Who Should Attend:

- Directors, group leaders, managers, and senior staff of QA/QC
- Directors, group leaders, managers, and senior staff of regulatory affairs
- Analytical chemists
- Formulation scientists
- Process development scientists
- CMC (chemistry, manufacturing and control) managers and directors

Presenters

Tim Watson, PhD
Research Fellow
GCMC Advisory Office
Pfizer

Mark Argentine, PhD
Senior Research Advisor
Analytical Sciences R&D
Eli Lilly

Hildegard Brümmer, PhD
Operational Laboratory Manager
SGS Life Science Services, Berlin

Moderator

Patricia Van Arnum
Executive Editor
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What is a Vapor?

Figure 1. Water phases.

FIGURE IS COURTESY OF THE AUTHORS.

There are three primary states of matter—solid, liquid, and gas. The term "vapor" is defined in several ways. Scientifically, a vapor is a gas at a temperature lower than its critical point; a vapor is a gas phase where the same substance can also exist as a liquid. An example is atmospheric water vapor. At temperatures above the dew point, water in the atmosphere is a gas. As the temperature is lowered through the dew point, the gaseous water condenses to form a fog or mist, or it can condense and form liquid water on a cold surface. Another definition of vapor is visible moisture in the air, as in fog or steam—a system in which a liquid is suspended in a gas.

Figure 1 shows water in various phases: the lake, the dense fog at the foot of the mountain, the wisps of cloud, and the blue sky above. The lake is certainly liquid water; the blue sky is just as clearly a gas which contains water in the gaseous state. The fog or cloud in the center is a mixture of a gas phase (comprised of nitrogen, oxygen, water, carbon dioxide, and trace amounts of inert gases) and a suspended liquid phase (small droplets of water). The density of the fog or cloud varies with its temperature. It is thickest (i.e., suspending the most liquid) near the base of the mountain where it is coldest. It is clearly less dense, with less suspended water droplets near the top of the image where the temperature is higher.

One of the major difficulties with hydrogen-peroxide (H_2O_2) processes is the use of a vapor for delivery of H_2O_2 and water (H_2O) to the target chamber. It must be understood that a vapor is a mixture of air and liquid that is present within the chamber. In decontamination or sterilization using H_2O_2, the liquid phase is comprised of both H_2O_2 and H_2O, and the concentration of each in the gas and suspended liquid state can vary across the system.

James P. Agalloco and James E. Akers

Peer-Reviewed—Weighing Potent Compounds – *contin. from page 45*

priate personal protective equipment, a written procedure, hands-on training on proper handling of potent compounds in a VBE, good handling practices, and an annual preventative maintenance program for both the dispensing system and the VBE.

Automated powder dispensing offers an efficient combination of both strategies of containment and improved sample handling techniques. Combining the dosing head, a HEPA-filtered VBE, and good potent compound handling techniques can eliminate the need to use an isolator to precisely weigh OEB 5 compounds for analytical testing. An added benefit is that any researcher can undergo simple training and be qualified to operate the automated system, which also removes user variability from the process. Overall, the use of the automated dispensing system in a VBE affords accurate and reproducible weighing of potent compound while keeping researchers safe and protecting the laboratory environment from contamination.

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Webcast: Safe automated weighing of potent compounds in the pharmaceutical industry

Roy Helmy, PhD, director of analytical chemistry at Merck Research Laboratories, and **Joanne Ratcliff, PhD,** communication project manager at Mettler Toledo AG, explain how the use of automated dosing, a high-efficiency particulate air (HEPA)-filtered ventilated balance enclosure (VBE), and good potent-compound handling techniques have eliminated the need to utilize an isolator to precisely weigh small quantities of occupational exposure band five (OEB 5) compounds for analytical testing. The webcast will provide insight on:

- How researchers can work in a laboratory environment with OEB 5 compounds without the need for an isolator
- How automated weighing of potent compounds can increase the safety of researchers while delivering accurate and reproducible weighing
- How automated weighing of potent compounds can be 20 times faster than the manual equivalent.

The webcast will be broadcast Sept. 17 at 11:00 am EST and available for on-demand viewing thereafter. For additional information, go to www.pharmtech.com/potent.

Application of Engineering Solutions to Solve Challenges in Pharmaceutical Processing: Case Studies from Development to Production Scale

ON-DEMAND WEBINAR

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EVENT OVERVIEW

Pharmaceutical manufacturing of solid oral dosage forms such as tablets and capsules involves several powder handling steps, including blending, transfer, granulation, fluid bed drying, tablet compression, and encapsulation. The inability to achieve reliable powder flow during these steps can have a significant adverse effect on the manufacturing a product. Production costs can be significantly higher than anticipated due to required intervention on the part of operators, low yield, or unplanned process redesign. Powder characteristics such as particle size distribution, bulk density, cohesiveness, stickiness, and static behavior can have a significant influence on manufacturing processes for small-scale or large commercial-scale operations. Low melting or softening solids can add another handling challenge in dosage form manufacturing, especially in cases where high speed tableting is required for large-scale manufacturing. The experience from multiple projects can help alleviate or solve many of these challenges regardless of the phase of the project.

Key Learning Objectives:

- Techniques to solve and prevent powder handling challenges.
- Innovative solutions to handle low melting, cohesive powders, and granulations in pharmaceutical manufacturing.

During this 60-minute interactive webcast, two industry experts will discuss challenges in powder and product handling such as flowability, stickiness, and the potential to soften or melt during the manufacture of solid dosage forms. They also will discuss the application of engineering solutions to overcome these processing challenges. Case studies will be shared to demonstrate possible solutions.

Anil Kane, Ph.D. Executive Director, Global Formulation Sciences, PDS at Patheon will discuss case studies in application of innovative solutions to solve critical powder handling issues in tableting/encapsulation.

James Prescott, Senior Consultant/Director, Jenike & Johanson, Inc., will discuss the use of bench scale tests to predict powder flow and segregation behaviors at production.

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- Formulation scientists
- Formulation R&D managers, directors, and group leaders
- Process development scientists
- Process development managers, directors, and group leaders
- Section Heads
- Project Managers
- Technical personnel involved in formulation and development
- Scientists, manager, directors, and group leaders involved with formulation
- Manufacturing managers
- Technical personnel involved with QA/QC
- Technical personnel responsible for production scale work
- Process Engineers

Presenters:

Anil Kane, Ph.D.
Executive Director,
Global Formulation Sciences, PDS
Patheon

James K. Prescott
Senior Consultant and Director,
Jenike & Johanson, Inc

Moderator:

Rita Peters
Editorial Director,
Pharmaceutical Technology

For questions, contact Kristen Farrell at kfarrell@advanstar.com

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Outsourcing Partnerships for CMC Development

Jim Miller

Are strategic partnerships in clinical research a model for CMC services?

The first generation of strategic sourcing relationships in clinical research is coming up for renewal, and the CRO industry is watching carefully to see how they renew. Strategic sourcing relationships, which involve global bio/pharmaceutical companies contracting large portions of their clinical research programs to the largest CROs, have transformed the clinical research industry. CROs that have won strategic relationships, including Icon, Parexel, Quintiles, and Covance, now control substantial shares of the clinical research market while smaller CROs have been forced to fight over the "leftovers" from mid-size and emerging bio/pharma companies.

All indications are that clients are happy with most aspects of their strategic sourcing relationships. For the most part, these arrangements are delivering on their promise to the global bio/pharmaceutical companies, especially lower costs, better trial execution, and reduced staffing. Given their performance and the high costs that would be involved in switching vendors, it is likely that most (probably all) of these deals will renew.

That's good news for the CROs that have been able to secure these strategic relationships. Not only have they received the project volumes negotiated in the original deals, they have received work well beyond the original scope, including projects in adjoining activities that were not part of the initial arrangement. As a result, their revenues have been growing at the annual rate of 15–20%. Profits have not grown as quickly due to the costs of expanding capacity to handle the burgeoning volume, but margins are expected to improve over time.

CDMOs should be thinking about when and if the clinical-research model will be adapted to CMC services.

Suitable for CMC development?

Given the success of the strategic relationships in clinical research, CDMOs should be thinking hard about when and if that model will be adapted to chemistry, manufacturing, and control (CMC) services. If it can be ported into the CMC environment, the model could drive a radical restructuring of the industry by creating big opportunities for some CDMOs but also shutting out others, which would result in a flurry of acquisition activity. Whether the model can be fully adapted to the CMC world, however, is open to question.

Perhaps the biggest difference between clinical research and CMC development is that CMC development is all about creating knowledge, innovation, and intellectual property that ultimately differentiates a product in the market. CMC creates a lot of knowledge about the molecule, some of which is captured in laboratory data but much of which is generated and understood less formally, just by working on the process or product. Further, CMC development generates innovations such as more efficient processes for manufacturing APIs or improved formulations to aid drug delivery.

Bio/pharmaceutical companies recognize that knowledge and innovation creation is part of CMC development, and companies are understandably reluctant to give it up entirely. They want to retain the knowledge that is generated and want to own or protect the intellectual property (IP) that is created.

By contrast, clinical research is only about collecting and analyzing data on the effectiveness and safety of the product in the patient. It seldom leads to product innovation directly (the famous case of Viagra [sildenafil citrate], first discovered as a cardiovascular drug and later developed as a treatment for erectile dysfunction, is the rare exception), and the information technologies that clinical research leverages are not core competencies for bio/pharmaceutical companies.

Another major characteristic of CMC development that may mitigate against strategic partnerships is the diversity of technologies and know-how that are used to develop a drug. It would be uneconomical and infeasible for a

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CMC-services provider to acquire and maintain all of the technologies used to manufacture or deliver a drug. Think of all the possible types of reactions used to synthesize small-molecule compounds, and the way certain companies have carved out special niches for themselves for technologies such as high-energy reactions that are only appropriate in particular circumstances. Similarly, expertise and equipment for solubility-enhancing technologies such as spray drying or micronizing is concentrated in a few specialty CDMOs that can efficiently service the limited number of candidates that need that expertise.

The diverse range of technologies would seem to guarantee that bio/pharmaceutical companies will always need a wide array of CMC service providers to meet their development requirements.

Strategic models

The nature of CMC development would suggest that it may not be as suited to the strategic partnership model as clinical research. While there are some CMC activities that have gone a long way to adopting that model, namely clinical packaging and analytical testing, those activities have more in common with clinical research. Neither of those activities generates IP and both require more operational expertise than scientific expertise.

As the bio/pharmaceutical industry continues to adapt to a changing market and scientific environment, however, some of the forces that have driven strategic clinical research relationships may come to bear on CMC development as well. Consider global reach. CMC expertise is more widely available, especially for small-molecule API development and for basic formulations. As cost pressure increases, companies seem to be more open to exploring CMC development in lower-cost locations. Further, global bio/pharmaceutical companies recognize the need to develop products specifically for those emerging markets.

At the same time, information technology has made collaboration and knowledge-sharing possible over great distances, so the opportunity to disperse those activities may be increasing. CMC providers with truly global operations that can access and network lower-cost resources in emerging markets might be able to build favorable positions as strategic providers.

The other big opportunity for strategic partnerships may lie in integrated service offerings. Time and cost are of the essence in drug development today, and companies offering a combined service developing an API and drug product may be able to offer significant reductions in both. One-stop offerings have the potential to reduce the leakage of knowledge as projects are handled off from one provider to another, and they can eliminate or reduce the periods of inactivity between development activities. Delivering the promise of one-stop models, however, will require a level of operational excellence that few in the CMC industry have yet been able to achieve. **PT**

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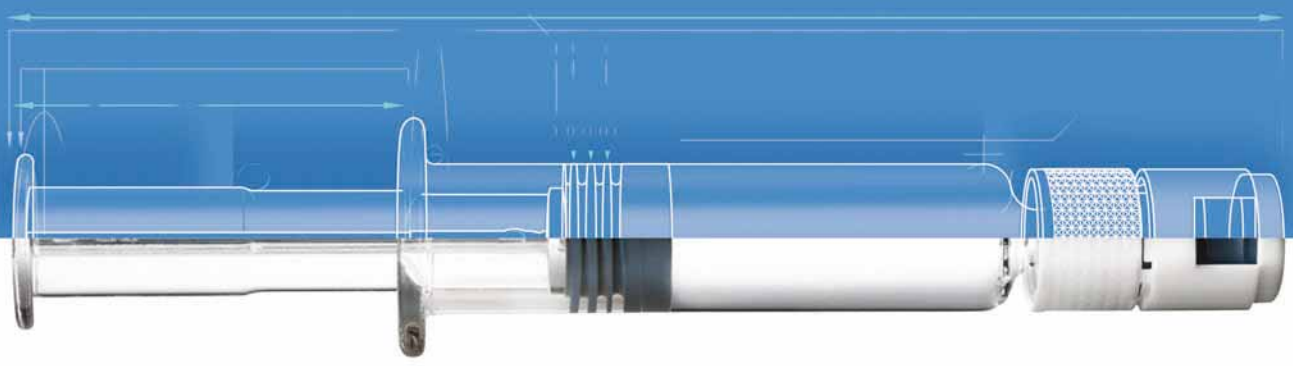
From clinical development to commercial production



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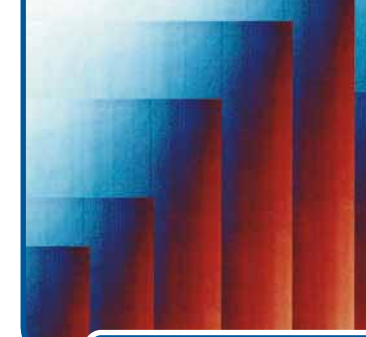

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The Basics of Measurement Uncertainty in Pharma Analysis

Chris Burgess

How good is a reportable value?

All measurements are subject to error. When a reportable value is derived from a measurement or series of measurements, this value is only an estimate of the "true" value and has a range around it associated with how confident one is that the true value lies within it. Traditionally in the pharmaceutical industry, a range is selected corresponding to 95% confidence (1).

Reportable value data quality

The quality of a reportable value or an analytical result depends upon the size of the confidence interval. The smaller the confidence interval is, the more confident one is in relying on one's reportable value or analytical result. Unfortunately, also for historical reasons relating primarily to physical metrological considerations, the International Organization on Standardization (ISO) uses the term "measurement uncertainty" (MU) for the same concept (2).

One difference between the ISO MU approach and the International Conference on Harmonization (ICH) Q2(R1) and *United States Pharmacopeia* (*USP*) approaches is that in the latter, the effects of imprecision and bias are considered separately (3). It should be noted, however, that the *USP* General Chapter <1225>, "Validation of Compendial Procedures," and related General Chapters <1224>, "Transfer of Analytical Procedures," and <1226>, "Verification of Compendial Procedures," are under revision at present (4-6).

USP General Chapter <1010>, Analytical Data—Interpretation and Treatment, clearly states that accuracy has a different meaning from ISO (7). The *USP* states, "In ISO, accuracy combines the concepts of unbiasedness (termed trueness) and precision," and USP further defines a conventional 95% confidence interval around the mean of

$$\bar{X} \pm t_{(0.05,\ n-1)} \frac{S}{\sqrt{n}}.$$

The term $\frac{S}{\sqrt{n}}$ is the standard error of the mean and is called the standard uncertainty in ISO.

$t_{(0.05,\ n-1)}$ is called the coverage factor.

$t_{(0.05,\ n-1)} \frac{S}{\sqrt{n}}$ is called the expanded uncertainty in ISO.

Another difference is the way in which the standard deviation (s) is calculated. The ISO approach is by means of a calculated error budget (8), whereas the ICH Q2(R1) relies upon information derived from an experimentally designed analytical trial (3). Theoretically, these two approaches should yield similar results. In practice, however, this is not always the case. ISO also uses a different nomenclature from ICH. What would usually be called the analytical measurement or result is called in ISO the measurand. This measurand is the particular quantity subject to measurement and is related to the measured analytical response function by means of an equation in the same way as an analytical result.

Concept of an error budget

The idea behind an error budget is that if all sources of error are known, it is possible to calculate an estimate of the uncertainty of the measurand or reportable value based upon converting all the errors to standard deviations and then combining the variances. If all the error processes are independent, then an error budget can be defined in five steps:

- Define all the process elements involved and their interrelationships
- Define the measurand in terms of these process elements
- Identify all error sources and group them as required
- Estimate their individual contributions and convert them to standard deviations and combine them to produce an overall estimate of standard deviation
- Estimate the overall uncertainty using an appropriate coverage factor as described previously.

Figure 1 shows the error budget process diagrammatically.

An example of a simple error budget for a standard solution. The error budget approach may seem rather daunting, but a simple example of the preparation of a standard solution will make things clearer. This example is a common task in the laboratory, but few calculate how good their standard solutions are.

The reference standard purchased has a certified purity of 99.46 ± 0.25. Approximately 100 mg of this reference standard is weighed, by difference, accurately using a five-place analytical balance. The reference standard is dissolved in water, and a solution is made up to the mark with water in a Grade

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A 100.0 mL capacity volumetric flask at ambient laboratory temperature. It is assumed that the laboratory temperature is controlled but may vary between 16 °C and 24 °C. The first step is to draw a flow diagram of the analytical process used to prepare the standard solution. This diagram is shown in **Figure 2.**

Identify the measurand. In this instance, the measurand (C) is the concentration of the reference material in the standard solution in mg l^{-1} and is defined by the equation:

$$C = \frac{mP}{V} 1000 \text{ mg} 1^{-1}$$

where m is the mass of reference material in mg. P is the purity as a mass fraction of the standard, and V is the volume of the volumetric flask in mL.

Identify the error sources. Based upon the analytical process flow (see **Figure 2),** one can now identify three main areas of error, namely, the reference stand itself, the weighing process and the solution, and the final volume of the solution. It is helpful to use a Ishikawa diagram to aid the identification and grouping of error sources. For this example, the Ishikawa diagram is shown in **Figure 3.** In **Figure 3**, the possible sources of error are shown for each of the three groups. In this example, it is assumed that the reference standard is sufficiently homogeneous to ignore any error contribution and is freely and easily soluble in water.

Note that the volume of the solution has three distinct uncertainty components that need to be taken into account:

- The uncertainty in the marked calibration volume of the volumetric flask itself at 20 °C
- The difference between the calibration temperature of the flask and the temperature at which the solution was prepared
- The uncertainty associated with filling the flask to the calibration mark.

Not all error contributions are of equal importance. To find out which error contributions are of importance, however, it is essential to convert all errors to standard deviations (8).

Figure 1: Error budget process.

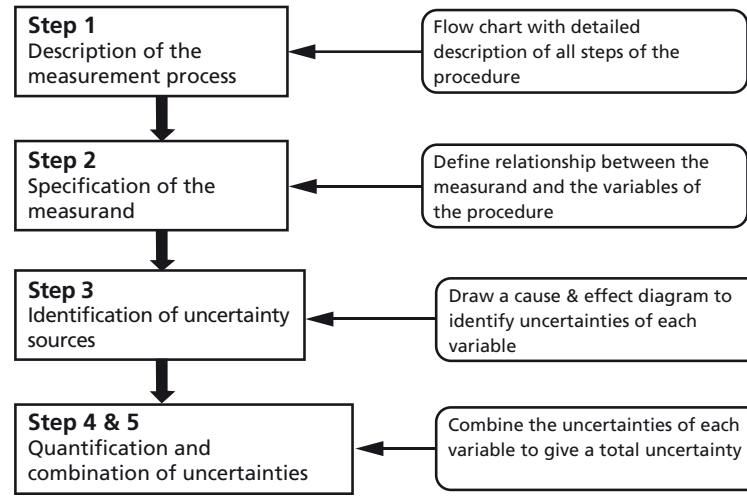
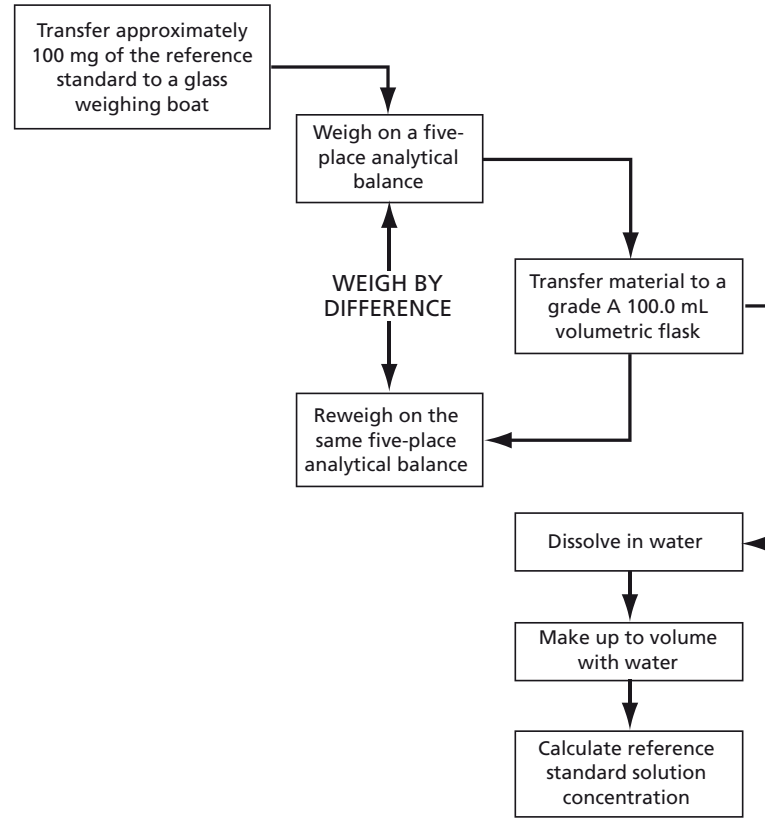


Figure 2: Analytical process flow for preparing the standard solution in our example.



Processes to convert specifications, ranges, and measurement data into a standard deviation. The easiest method to evaluate the standard deviation is by the statistical analysis of series of observations and assume the normal distribution. In the example, this method would be used in determining the uncertainty of filling the volumetric flask to the mark. This direct determination is known as a Type A uncertainty.

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Figure 3: Ishikawa diagram for our analytical process.

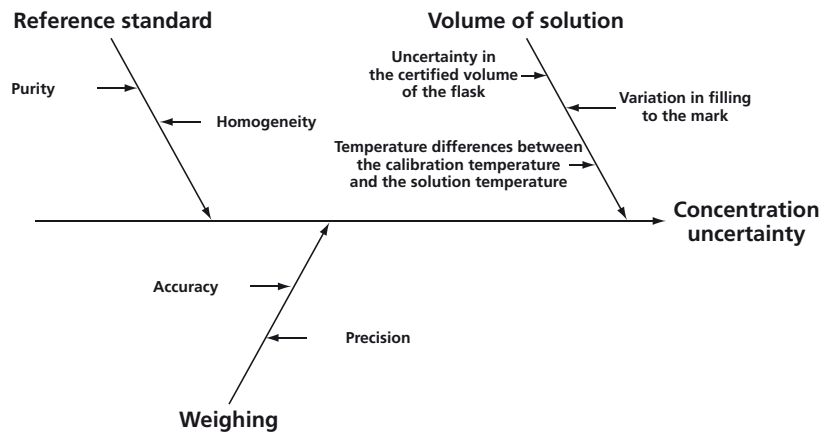

Table I: Combined uncertainty for the measurand C.

Description	x	Value x	U_x		$\frac{u_x}{X}$	
Purity of reference standard	P	0.9946	U_P	0.001443	$\frac{u_P}{P}$	0.001443
Mass of the reference standard mg	m	100.28	U_m	0.05	$\frac{u_m}{m}$	0.0005
Volume in the flask ml	V	100.0	U_V	0.07	$\frac{u_v}{V}$	0.0007

Type B uncertainties are derived from two approaches:

- Converting certificate ranges where there is no knowledge of the shape of the distribution so the rectangular distribution is assumed. For a range of ± a, the corresponding estimate for the standard deviation would be $a/\sqrt{3}$ In the example, the uncertainty in the purity of ± 0.25 would be converted using the rectangular distribution.
- If it is more likely that the value lies closer to the central value, then the triangular distribution is assumed. For a range of ± a, the corresponding estimate for the standard deviation would be $a/\sqrt{6}$ In the example, the uncertainty in the grade A volumetric flask of ± 0.10 would be converted using the triangular distribution.

Uncertainty contributions in the example. Now we can proceed to quantify all the uncertainties in our analytical process in the following manner:

Reference standard uncertainty, u_P. Using the rectangular distribution we have:

$$u_P = \frac{0.0025}{\sqrt{3}} = 0.001443$$

Note that the purity and it uncertainty have been converted to mass fractions.

Weighing uncertainty, u_m. Using the balance manufacturer's data (Type A) we have:

$$u_m = 0.05 \text{ mg}$$

Note that our actual value of weighed material was 100.28mg.

Volumetric uncertainty (u_V). Here we have three different contributions to u_V:

- The flask itself using the triangular distribution:

$$u_{vc} = \frac{0.10}{\sqrt{6}} = 0.04 \text{ mL}$$

- The temperature effect assuming the coefficient of expansion of water of 0.00021 °C-1 and assuming the rectangular distribution:

$$\text{Volume variation} = \pm(100(4)(0.00021)) = \pm 0.084 \text{ mL}$$

$$u_{vT} = \frac{0.084}{\sqrt{3}} = 0.05 \text{ mL}$$

and the Type A uncertainty associated with the filling of the flask to the calibration mark. This was determined by the filling repeatability for n=6 assuming a normal distribution; u_{vr}=0.02 mL.

One can now combine these three standard deviations to arrive at the overall volumetric uncertainty

$$u_v = \sqrt{u_{vp}^2 + u_{vr}^2 + u_{vT}^2}$$
$$= \sqrt{(0.04)^2 + (0.02)^2 + (0.05)^2}$$
$$= 0.07 \text{ mL}$$

Finalising the error budget. Now that all uncertainties have been converted into standard deviations, they can be combined to produce an uncertainty for the measurand C as shown in **Table I** and using the variance combination equation:

$$\frac{u_c}{C} = \sqrt{\left(\frac{u_p}{P}\right)^2 + \left(\frac{u_m}{m}\right)^2 + \left(\frac{u_v}{V}\right)^2}$$
$$= \sqrt{(0.001443)^2 + (0.0005)^2 + (0.0007)^2}$$
$$= 0.00168$$

It is important to note that the uncertainty contribution from the reference standard is greater than either the weighing or the volumetric errors.

Expression of confidence: calculating the reportable value and its uncertainty. The concentration of the reference standard solution is directly available from the measurand equation:

$$C = \frac{mP}{V} 1000$$
$$= \frac{100.28(0.9946)}{100.0} 1000$$
$$= 997.4 \text{ mg1}^{-1}$$

The uncertainty in the measurand u_c and the expanded uncertainty U are now readily available.

contin. on page 73

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Handheld analyzer

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

Fluid-bed dryer

Federal Equipment offers a Vector fluid-bed dryer–granulator with a multipurpose Flo-Coater system. The unit has 316-L stainless steel product-contact surfaces, 20- and 60-L spray-granulation bowls with expansion chambers and guns, a two-bar internal shock rating, a top blow-out feature, an air-handling unit with filter, and a 15-hp blower. Other features include a dehumidification package, a dew-point monitor, and programmable logic controls. **Federal Equipment,** *Cleveland, OH • www.fedequip.com • tel. 216.271.3500*

Tablet press

The FE35 is a single-rotary tablet press that uses up to 51 stations to produce over 367,000 tablets/hr. The machine is clad in easily detachable, FDA-certified high-performance polymer panels, and offers 360-degree access. The FE35 contains geometrically optimized surfaces that are designed to offer the easiest-possible handling and fast cleaning. **Fette Compacting America,** *Rockaway, NJ • www.fetteamerica.com • tel. 973.586.8722*

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Ross Inline High Shear Mixers

The mixers are a versatile choice for general purpose mixing, powder wet-out, particle size reduction, solubilization, emulsification, and homogenization. This device features a four-blade rotor running within a close tolerance fixed stator at tip speeds in the range of 3,000-4,000 ft/min, with ultra-high shear designs running at tip speeds over 11,000 ft/min. **Ross, Charles & Son Company,** *Hauppauge, NY • www.mixers.com • tel.* 800-243-ROSS

Biowelder® TC

The Biowelder® Total Containment (TC) by Sartorius Stedim Biotech features innovative technology that permits sterile connection of liquid-filled thermoplastic tubing that has an outer diameter (OD) of up to 1 inch. This is used on disposable bags or bag assemblies in all biopharmaceutical manufacturing processes. The sterile welding process is fully automated and can be performed in non-classified or classified environments while maintaining product sterility. **Sartorius Stedim North America,** *Bohemia, NY • www.sartorius.com • tel. 631.254.4249*

Tooling storage box

Natoli's tooling storage boxes are intended for storing, transportation, and cleaning of tooling while being safely secured in a single container. Unlike other boxes, the secure-fit lid allows safe stacking. The removable tray with optional Handle & Leg Kit can be transferred directly into ultrasonic cleaning units and other applications, and the patented design protects tooling from rust and water spots. **Natoli Engineering Company,** *St. Charles, MO • natoli.com/storage • tel. 636.926.8900*

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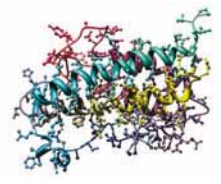
Vacuum-recovery system

VAC-U-MAX's Vacuum Recovery System for Granular Activated Carbon (GAC) conveys the spent carbon material from holding tanks to waste containers. The VAC-U-MAX self-contained GAC delivery system is mounted on a self-contained skid. The system features a prepackaged, dilute-phase, pneumatic-conveyor system to deliver or remove GAC from scrubber towers and holding tanks. The system includes tubular probing wands, a convey hose, a filter receiver, a vacuum pump, and a control panel. **VAC-U-MAX,** *Belleville, NJ • www.vac-u-max.com • tel. 973.759.4600*

Industrial controls and automation

Ross SysCon is branching out to more applications in the pharmaceutical, food, cosmetics, plastics, adhesives, chemicals, coatings, paper, energy, and utilities industries. In one of its most recent projects, Ross SysCon supplied seven (7) NEMA 4X stainless steel enclosures with a RX3i multi-rack programmable logic controller (PLC)-based platform to a nuclear power plant facility. **Ross, Charles & Son Company,** *Hauppauge, NY • www.mixers.com • tel.* 800.243.ROSS

OUTSOURCING & CONSULTING SERVICES



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SGS Life Science Services offers analytical chemistry, microbiology, stability studies, method development, protein analysis, and bioanalytical testing. With the acquisition of M-Scan's laboratories, SGS's portfolio now includes the characterization of biologics with GLP–GMP contract analytical services, consulting, and training based on mass spectrometry and chromatography. **SGS Life Science Services,** *www.sgs.com/lifescience • tel. 866.747.5003*

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Laboratory cleaning system

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STATISTICAL SOLUTIONS – *contin. from page 64*

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The coverage factor of k=2 corresponds to a confidence of 95.45%

Based upon this expanded uncertainty, we calculate that we have confidence that the standard solution uncertainty is approximately 0.34%.

Summary

This article covered some of the basics of error budgets and carried out a calculation of an expanded uncertainty for a standard solution. The expanded uncertainty is small (0.34%) and is dominated by the contribution from the reference standard itself. The more complex the analytical procedure, however, the more expanded uncertainties will build.

In regulated laboratories, such as the Official Medicines Control Laboratories in Europe, it is a prerequisite that analytical tests are performed under a properly functioning quality system, which means that:

- All balances and volumetric glassware are under regular control
- Official reference substances or in-house reference substances are properly qualified and stored
- Instruments are regularly calibrated
- Equipment is regularly requalified
- Laboratory technicians are (re-) qualified.

The uncertainties due to these sources are under control and are assumed to contribute little to the total uncertainty of the test result (9).

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Ad Index

Multivariate Approaches for Powder Characterization

John Yin, an applications specialist with Freeman Technology, discusses the importance of powder-characterization techniques for optimizing pharmaceutical product development and manufacturing processes.

Q. Why is powder characterization so important for the pharmaceutical industry?

A. Understanding and characterizing powder behavior is critical for the production of solid-dosage formulations, and there are many key properties of powders that determine how they will behave in a hopper, when being filled into a die, and compressed into a tablet. Understanding the variables and processing conditions involved in relation to what powders are required to do, therefore, is relevant during all aspects of development and manufacturing and can provide information that can be used for formulation development, process optimization, and improvement of the quality of the final drug product.

Q. What advances in powder characterization have been achieved in recent years?

A. In the past, much of the focus on powder characterization has been at the single aspect level where one standard or number is expected to dictate 'good' or 'bad' once and for all. In reality, we rely on multiple techniques for explaining behavioral differences when being subjected to many processing conditions. While some information can be obtained with traditional methods, such as bulk-tapped density, flow through an orifice, and angle of repose, these techniques are not at all representative of the conditions that powders see under process conditions and, therefore, are not able to provide process-relevant and differentiating information given the process technologies in use today in the pharmaceutical industry.

The multivariate approach for characterizing powders has made it possible to gain much greater insights into how the combination of powder physical properties and external variables affect their behavior. Dynamic testing for example, which measures the flow energy of a powder with respect to external conditions, such as aeration, flow rate, and consolidation, is a newer technique enjoying considerable industrial uptake. Advances in shear testing are also improving both the precision and reproducibility of this important analytical method.

Q. What limitations remain with respect to powder-characterization technology for the pharma industry? Why are these issues important?

A. One of the biggest limitations at this point is the lack of understanding of powder behavior at the level needed to describe such behavior mathematically or from an axiom perspective. There are so many variables, not just particle size and density, which are often perceived as the only critical factors that influence powder behavior, but also the surface texture, particle shape, stiffness, and porosity as well as external influences, such as air, moisture, consolidation stress, and flow rate, which can all contribute to the picture. There is much work to be done in this area and it will be a steep learning curve. A second challenge is the need to make the pharmaceutical industry and other powder-processing industries (that share similar challenges) aware of the benefits of more comprehensive powder characterization.

Q. What advances in powder-characterization technology might be expected?

A. The adoption of continuous manufacturing for the production of solid dosage forms will have an impact on powder-characterization technology. In addition, as the amount of data gathered on different powder systems increases, we will continue to gain more knowledge about powder properties and behavior and be able to expand our insight into performance with respect to different processing conditions. **PT**

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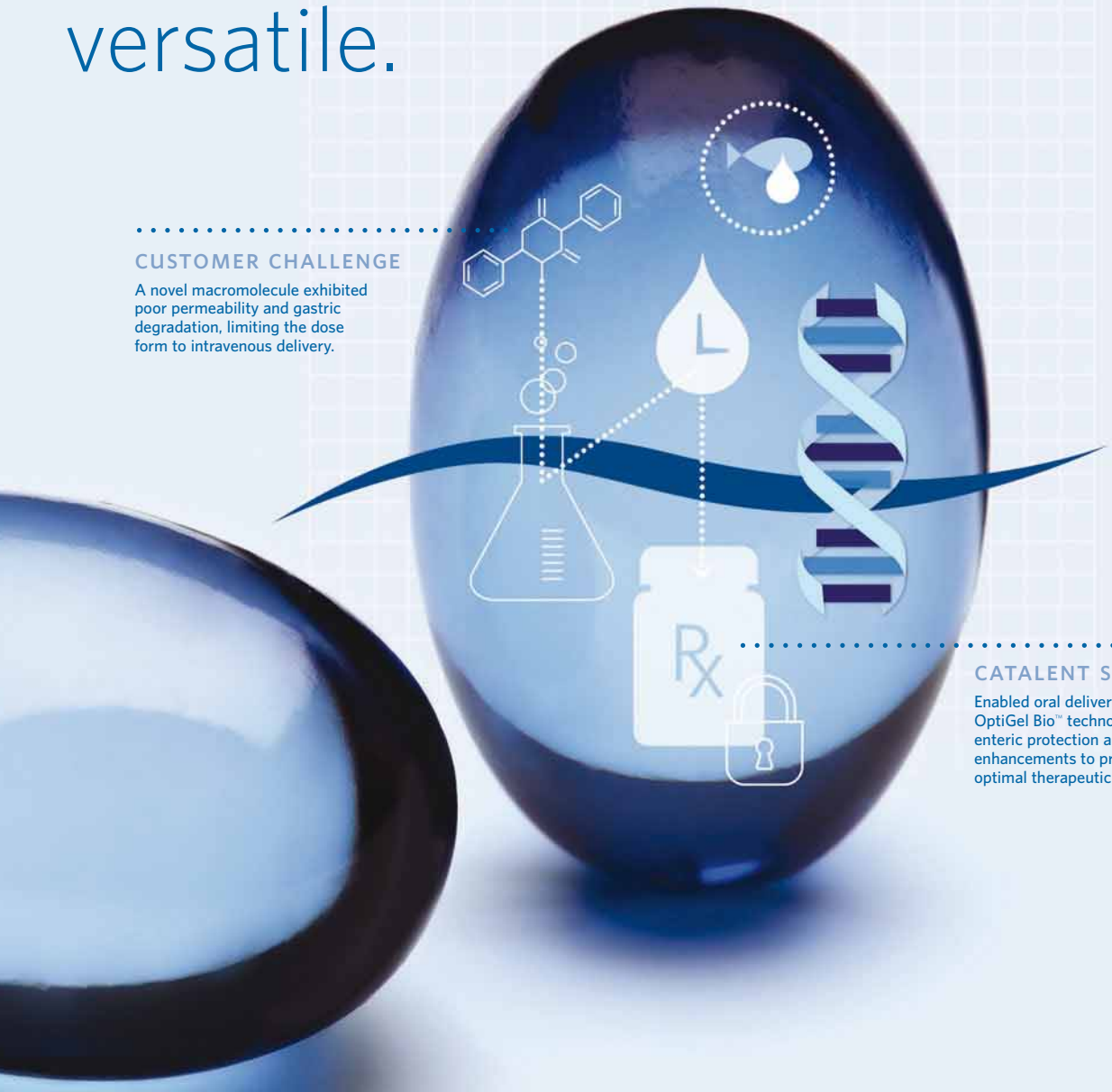

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