Volume 38 Number 7
PHARMACEUTICAL TECHNOLOGY
JULY 2014
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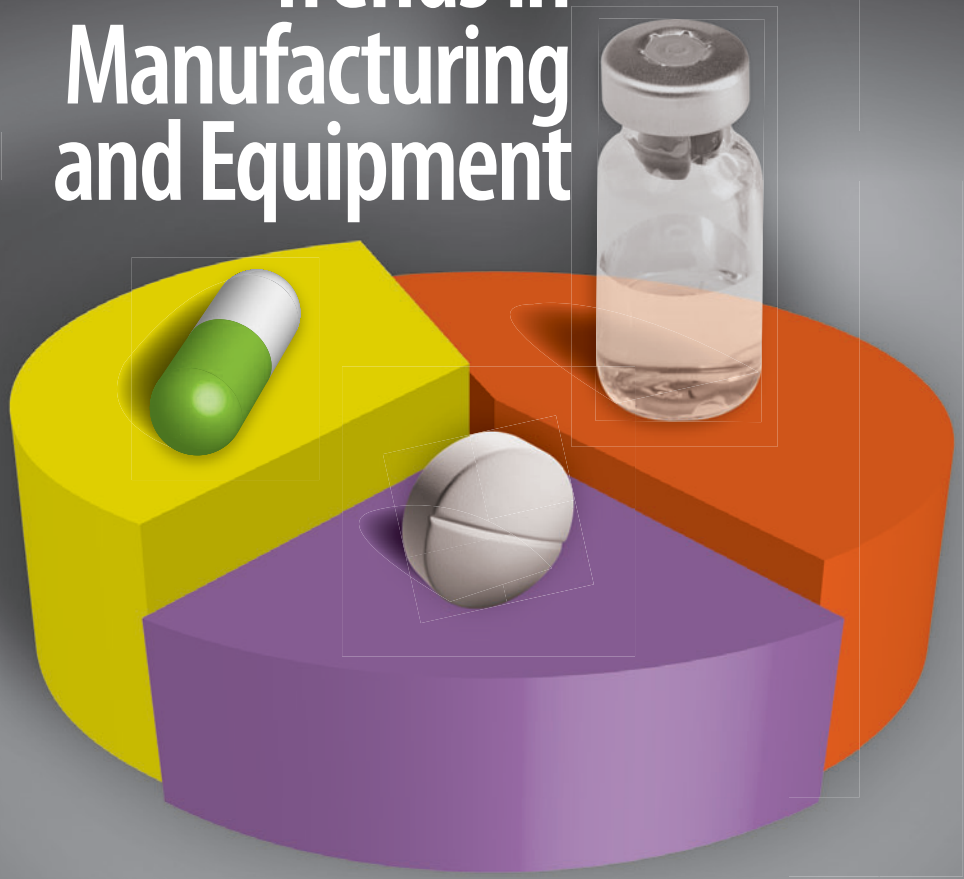
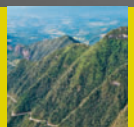
Trends in Manufacturing and Equipment



PEER-REVIEWED

Cleanability of Pharmaceutical Soils from Different Materials of Construction

API SYNTHESIS & MANUFACTURING
Continuous Flow API Synthesis



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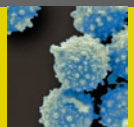

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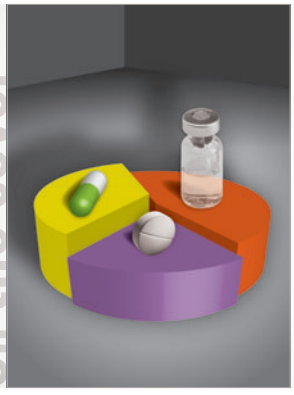

COVER STORY

28 Trends in Manufacturing and Equipment

Survey shows gains in process analytical technology and indicates areas for future innovation.

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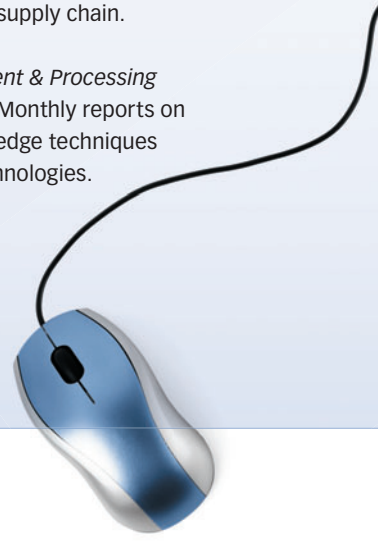

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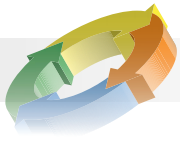

CLEANING VALIDATION

36 Cleanability of Pharmaceutical Soils from Different Materials of Construction

The authors look at the cleanability of pharmaceutical soils from a variety of materials of construction to determine the relative ease of cleaning and explore potential grouping strategies as part of a comprehensive cleaning validation program.

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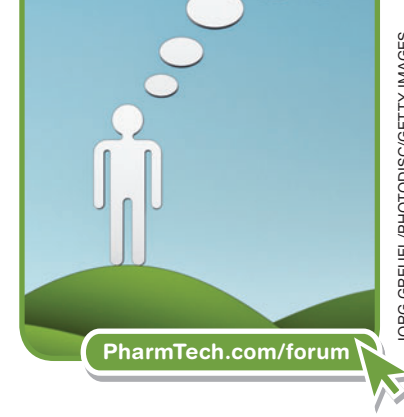

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Benefits and Risks of Drug Information on Social Media

Rita Peters

FDA draft guidances seek to maintain accurate drug information for patients in new media.

Social media has changed the way people and organizations communicate. Platforms like Twitter and Facebook have demonstrated that they can be effective tools for widespread communication of emergency instructions during natural disasters and in organizing political change in countries with censored media. Social media outlets, however, have limitations when asked to deliver complex, technical information. In addition, the open platform nature of the Internet presents challenges for companies trying to maintain correct information about their products online.

Noting that patients and healthcare providers regularly get information about medical products through social media outlets, FDA in June proposed two draft guidances that share the agency's current thinking about how drug and medical device manufacturers can accurately communicate about their products online.

So many words, so few characters

Guidance for Industry, Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices (1) provides recommendations for conveying information about a drug on social media platforms such as Twitter or paid search results links. While the 140-character limit of Twitter may be enough for the latest life updates from figures in popular culture, it will be difficult for drug companies to use the platform under FDA's proposed guidelines.

In the guidance, FDA notes: "… regardless of the platform, truthful, accurate, non-misleading, and balanced product promotion best serves the public health. For some products, particularly those with complex indications or extensive serious risks, character space limitations imposed by platform providers may not enable meaningful presentations of both benefit and risk … If an accurate and balanced presentation of both risks and benefits of a specific product is not possible within the constraints of the platform, then the firm should reconsider using that platform for the intended promotional message."

In the draft guidance, FDA indicates that a drug's risk information, including the most serious risk associated with the drug, must be presented with benefit information in the same limited-character message, such as a tweet. A mechanism, such as a hyperlink, must direct people to more information about risks. That is a lot of information to get into 140 characters.

Correcting misstatements

In *Guidance for Industry, Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices* (2), FDA explains that drug companies generally are not responsible for comments from third parties who are independent of the drug company that are posted on the company's website forum, an independent website, or in social media. The document notes approaches to correcting misinformation and posting corrective information.

If a firm voluntarily and truthfully undertakes the correction of misinformation that is within the scope of the guidance, "FDA does not intend to object if these voluntary corrections do not satisfy otherwise applicable regulatory requirements, if any," the draft guidance reads.

In a blog post (3), Thomas Abrams, director of FDA's Office of Prescription Drug Promotion for the Center for Drug Evaluation and Research, noted that the agency sees social media as an important resource and is committed to developing additional guidance for drug manufacturers, with the best interests of the patient in mind.

However, the task of maintaining proper information about regulated products in an unregulated environment may be too great a challenge for FDA or drug companies to manage.

Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rpeters@advanstar.com.

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1. FDA, *Guidance for Industry, Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices, Draft Guidance* (Rockville, MD, June 2014).
2. FDA, *Guidance for Industry, Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices, Draft Guidance* (Rockville, MD, June 2014).
3. FDA, FDA Issues Draft Guidances for Industry on Social Media and Internet Communications About Medical Products: Designed with Patients in Mind, blogs.fda.gov (Accessed June 17, 2014) **PT**

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HEADLINES ON PHARMTECH.COM/NEWS

- In a statement issued on June 20, Shire confirmed that the board had rejected a May 30, 2014 "unsolicited and highly conditional proposal" from AbbVie regarding a possible cash and share offer for Shire. Reuters estimated the value of the offer at $46 billion. Shire reports that the offer undermined the value of the company and its prospects, and the board had concerns with execution risks associated with the proposed structure, as AbbVie would redomicile in the UK for tax purposes.

- FDA has reported that Dr. Reddy's Laboratories has initiated a voluntary recall for Metoprolol Succinate Extended Release Tablets, USP 25 mg, 100-count bottle for failed dissolution specifications. The recall, initiated on May 23, 2014, involves 13,560 bottles, was for failure of a dissolution test observed at an 18-month time point, and involved two lots. FDA classified the recall as Class II, a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

- The National Institutes of Health (NIH) and the National Science Foundation (NSF) have collaborated on the I-Corps at NIH, a pilot program of the NSF Innovation Corps tailored for biomedical research. The program will train NIH-funded researchers to evaluate the commercial potential of scientific discoveries to further biomedical innovation. I-Corps is a nine-week boot camp where researchers are paired with instructors that have biomedical business experience and take a scientific method approach to customer discovery. Academic researchers and entrepreneurs with Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) Phase I awards from participating NIH institutes will be eligible to apply to I-Corps at NIH.

- A new jobs report published by EP Vantage revealed that Big Pharma employment dropped by 3% between 2003 and 2013, relieving fears that industry consolidation and restructuring would lead to significantly reduced headcounts and payrolls. The new report shows that when it comes to pharmaceutical industry jobs, big biotech and specialty drugmakers are growing in significance, more than offsetting the loss of jobs in Big Pharma. Headcount more than doubled over the past decade at companies with market capitalizations of more than $30 billion, but who are not traditionally considered Big Pharma.

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Industry Seeks Clearer Standards for Track and Trace

Stakeholders face challenges and benefits from a more secure pharmaceutical supply chain.

Beginning Jan. 1, 2015, manufacturers and distributors will need to have in place systems able to transmit information on prescription drug movement in the United States from plant, to packagers and various wholesalers and distributors, and ultimately to dispensers. FDA is charged by the Drug Supply Chain Security Act (DSCSA), a key component of the Drug Quality and Security Act (DQSA) of 2013, to issue guidance and rules for establishing such a process and is consulting with all stakeholders on viable approaches and policies (1).

FDA held a public workshop in May 2014 (2) to gain input from manufacturers and other supply-chain parties on developing standards for what eventually will be an interoperable tracking system for prescription drugs. FDA officials and industry leaders further reviewed DSCSA requirements, along with broader supply-chain security issues, at a June conference in Washington, D.C. sponsored by the Parenteral Drug Association (PDA).

The larger aim of drug tracking is to prevent drug diversion and to keep counterfeit and substandard products out of the US supply chain, observed Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), in opening the FDA workshop (2). Woodcock cited the recent discovery in the US of counterfeit drugs to treat cancer, hypoglycemia, and hormone replacement, and noted the dangers of stolen or diverted products entering the distribution system. Electronic tracking, Woodcock noted, also would help manage product recalls, prevent shortages, and deter criminal elements from introducing substandard drugs into the US market.

Seeking guidance

FDA is working with supply-chain parties to tackle its multiple assignments under DSCSA, starting with guidance on how manufacturers and distributors should identify suspect products and then notify other parties that such products are not legitimate. More challenging is a November 2014 deadline for draft guidance that sets standards for interoperable exchange of required information. That includes transaction information (TI), transaction history (TH), and transaction statements (TS)—the "3Ts"—every time a product changes hands. Initially, data will apply to drug lots, as opposed to individual packages, and can be provided via paper or electronic systems. Supply-chain participants have to maintain data records for six years, and they have to be able to provide drug transaction information fairly quickly when requested by FDA or other agencies or is needed to notify trading partners when illegitimate products are detected. By 2017, manufacturers will need unique identifiers on drug packages and electronic data transmission. A fully electronic package-level tracing system is set for 2023, most likely based on the Electronic Product Code Information Services standard.

There is broad agreement among supply-chain parties that clear standards are crucial to success, but considerable debate about crafting the specifics. Woodcock noted at the FDA workshop that it's difficult to reach agreement on standards, formats, and practices because that usually requires some parties to change what they're doing. Workshop participants indicated a need for clearer definitions of basic concepts, such as "efficient interoperability" and "electronic data interchange." There was discussion about use of packing slips to identify the contents in shipments, which is common practice for manufacturers, but raised objections from wholesalers that reliance on packing slip information would slow down the distribution process.

There also was debate over using email to send transaction information, an approach that seems simple and direct to some parties, but raises concerns about security and data control for others. Similarly, participants considered whether transmission of a PDF document constitutes dissemination of an electronic or paper document. Electronic transactions that disclose product prices are a concern for manufacturers, who fear that such information could encourage pilferage or theft and undermine rate negotiations.

Some stakeholders questioned the viability of the envisioned step-wise data transmission system called for by the legislation. An alternative suggestion was for all parties to submit information to a centralized data hub, which could provide records to determine if the product is legitimate when a problem arises, instead of each supply-chain partner passing and accepting thousands of product transaction reports. There also was a proposal that FDA limit its standards to what information has to be transmitted, and leave it to trading partners to figure out how to send data and messages. FDA officials agreed on the need for flexibility but also noted that the legislation requires the agency to issue standards for the program. Overall, stakeholders expressed strong interested in seeing FDA's policy earlier than November to help them meet the January 2015 implementation deadline.

Costs and benefits

While FDA crafts further guidance, manufacturers are preparing for both short-term and long-term changes, which are laid out in a DSCSA implementation timeline prepared by The Pew Charitable Trusts (3). Manufacturers already have spent millions of dollars on technology to implement drug serialization systems and anticipate that it will be costly and challenging to

integrate new technologies with existing operations, according to stakeholder perspectives on drug serialization and traceability, prepared for the Pew by Booz Allen Hamilton (4).

Pharmaceutical companies report that off-the-shelf software often is suitable to support databases and communication systems, although customization is needed to meet individual business needs. Most pharma companies plan to outsource systems development and implementation, and a host of IT consultants and vendors have emerged to tackle such projects.

Despite notable costs associated with serialization and tracking, there is optimism that such initiatives will translate into important gains for the industry. Not only will improved supply-chain visibility help block distribution of counterfeit or compromised pharmaceuticals, there is the potential for added business benefits, according to respondents to the Pew/Booz Allen study (3). In addition to facilitating drug recalls and enhancing cargo security, manufacturers anticipate gaining more timely and accurate production and shipping information. This information could help reduce production lead times, enhance inventory control, process returns more efficiently, prevent distribution of expired goods, help manage supplies for clinical trials, and improve tracking of drug samples. More detailed information on product movement through the supply chain, moreover, could help manufacturers ensure the accuracy of sales and chargebacks and support drug rebate reconciliation. Future gains might extend to improved accuracy in drug-reimbursement systems, better medication adherence by patients, and support for FDA reporting requirements for high-risk products. All together, these developments could support efforts to prevent drug shortages.

As standards emerge for a drug-tracking system in the US, policy makers are looking to facilitate policy harmonization with the European Union, China, and other nations. A broad goal is to agree on barcodes on pharmaceuticals that are acceptable in all markets. European governments are establishing unit-level tracking policies, with requirements for anti-tampering features on packages and guidelines for serialization and authentication. Most countries are adopting two-dimensional barcodes, although China may opt for a linear barcode requirement. Different requirements and implementation timelines in other regions, unfortunately, would add to the complexity of establishing pharmaceutical traceability systems that gain international acceptance.

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Susan Haigney
is managing editor of *Pharmaceutical Technology*.

Securing the Supply Chain

Regulators and industry leaders take on the task of securing the drug supply chain.

The pharmaceutical supply chain has been an increasing focus for regulators and the industry in the past couple of years. Drug shortages and counterfeiting have spurred the creation of legislation and industry guidelines to combat the situation and prevent suspect drug products from entering the market.

Regulators and Congress have stepped up in the fight against counterfeit and unsafe drugs by enacting legislation to ensure supply-chain safety. "The recent and upcoming changes to the FDA Safety and Innovation Act (FDASIA) have added a number of requirements intended to ensure a safe supply of medicines. Many of these enhancements are included in Title VII of the act, parts 701-718. The changes outlined in Title VII are important because they allow the agency to collect more comprehensive, accurate, and timely information about the pharmaceutical supply chain," says Susan Schniepp, vice-president, Quality and Regulatory Affairs at Allergy Laboratories.

In addition, Schniepp explains that FDASIA helps establish the same requirements for foreign and domestic manufacturers, allowing the agency to work more effectively with their overseas counterparts. The Act gives FDA tools to protect the integrity of the global supply chain. FDA can collect and analyze product data to enable risk-informed decision making on incoming products and partner with foreign authorities to leverage resources through information sharing and recognition of foreign inspections of facilities. "These changes have already resulted in two draft guidance documents: *Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration* and *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*," says Schniepp.

In June 2014, FDA issued draft guidance on how to identify suspect drug products in the supply chain (1). Developed under the Drug Supply Chain Security Act, the guidance describes potential signs that drug supply-chain stakeholders can look for to identify suspect drugs, including product labeling that may contain misspelled words or looks different than the standard labeling; packaging that has missing lot numbers or expiration dates or has been opened, damaged, or altered; or a change in shape or color from the standard product.

Supply-chain stakeholders are encouraged by FDA to be cautious when purchasing drugs from a new or unknown source, from the Internet, or purchasing drugs on the drug shortage list. Unsolicited offers for lower-priced drugs should also be avoided. The draft guidance provides supply-chain stakeholders with information on how to notify FDA of illegitimate products and details a process for stakeholders to follow when terminating previously made notifications.

Supply Chain Pilot Program

FDA initiated the Secure Supply Chain Pilot Program, in February 2014, to enhance the security of imported drugs. FDA published a notice in the *Federal Register* in August 2013 to solicit companies to voluntarily submit applications for participation in the program (2). Thirteen prequalified companies were designated to take part in the program. Participating companies received expedited entry for the importation of up to five selected drug products into the United States.

The companies met multiple participation conditions, including committing to comply with requirements of the Food, Drug, and Cosmetics Act; having a validated secure supply-chain protocol per the US Customs and Border Protection's Customs-Trade Partnership Against Terrorism program; having a plan in place to quickly correct potential problems FDA identifies regarding importation of specific products; having effective recall and corrective action plans in place; and maintaining control over their drugs from the time of manufacture abroad through entry into the US.

Supply-chain stakeholders are encouraged by FDA to be cautious when purchasing drugs from a new or unknown source.

"By creating incentives for manufacturers to adopt best practices for supply chain integrity, we can enhance the quality and safety of imported drugs," said Carol Bennett, acting director of the Office of Compliance in the FDA's Center for Drug Evaluation and Research, in a press release. "The program also allows the FDA to focus resources on the areas with the greatest potential risk to consumers."

"FDA's Supply Chain Pilot Program is designed to help in addressing the increasing issues and problems associated with importations that have arisen from the globalization of the pharmaceutical supply chain. The goal of the program is to expedite the importation of legitimate materials, APIs, and product coming from abroad. The pilot program will collect data from 2014–2016. At the end of this period, the data will be evaluated to establish a system where there is an efficient use of time and resources to evaluate items of importation. The system would rely on specific code numbers that would require little

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human intervention. Instead, time can be spent on evaluating the questionable materials that require a more detailed human review," says Schniepp.

Industry takes action

The pharmaceutical industry has also taken steps of its own to ensure the security of the drug supply chain. In 2009, the industry created Rx-360, a pharmaceutical industry supply-chain consortium that includes more than 80 companies and organizations. The consortium is committed to creating communication between pharmaceutical companies, suppliers, and contract manufacturers to better secure the pharmaceutical supply chain.

In an August 2013 interview with *Pharmaceutical Technology*, Rx-360 Chair Brian Johnson states, "Rx-360 believes that freely sharing information, such as alerts on potential supply-chain threats, is vital to the industry's success. Industry collaboration on sharing audit information and jointly conducting audits is crucial to improving the transparency of our increasingly complex and global supply chains" (3).

Organizations unite

The United States Pharmacopeial Convention (USP) is taking part in the "Fight the Fakes" campaign. The campaign is designed to spread awareness about the negative impact of fake medicines to create a global movement of organizations.

"Combating counterfeit and substandard products is an essential part of USP's mission to improving public health by promoting quality medicines around the world," said USP CEO Ron Piervincenzi in a press release. "The challenges we face today, with raw materials and finished products circling the globe before they reach the hands of patients and consumers, require collaboration to stem the tide of fakes" (4).

The campaign was established in 2013 and includes 25 healthcare groups, research institutes, foundations, nonprofits, and private sector organizations including the Generic Pharmaceutical Association, the Global Pharma Health Fund, the International Federation of Pharmaceutical Manufacturers and Associations, and the Partnership for Safe Medicines.

These continued efforts by regulators and the industry will hopefully prove to be a positive impact on the availability of medicines and the ensurance of patient safety.

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Supplier Audit Program Marks Progress

The Rx360 pharmaceutical supply chain consortium was launched in 2009 in response to the heparin adulteration crisis, which raised broad concerns about inadequate monitoring of the pharmaceutical supply chain by manufacturers. Since then, Rx360 has attracted more pharmaceutical and biotech companies to support its efforts to enhance supply-chain security. The group has expanded to conduct approximately 25-30 joint audits a year, a collaborative process that can lower audit costs, expand the audit process, and reduce suppler "audit fatigue." Joint audits coordinate the assessment of a particular supplier of APIs, excipients, container/closure systems, packaging materials, and other raw materials. All sponsors of the joint audit gain access to the resulting report, which then can be purchased by other parties.

To improve this program, Rx360 established a "strategic partnership" with BSI Supply Chain Solutions to handle joint audit scheduling and management. The goal is to conduct more than 100 joint audits in the coming year, said Martin VanTrieste, senior vice president at Amgen and founding chair of Rx-360. While the audit volume so far is respectable, he believes that there are thousands of suppliers that could benefit from this collaborative program. "But we're not close to that," he commented. Not all suppliers have bought in to the joint audit process, he notes, some due to fears the process could damage their relations with customers. VanTrieste also sees a reluctance within leading manufacturers to shift from doing audits themselves. The group's shared audit program has developed more slowly, but now has more than 200 audits available to members. Drug manufacturers and suppliers tend to feel more proprietary about their own reports on key suppliers, even with the ability to redact confidential information.

Rx-360 has formed an Asia Working Group to develop its program in China, primarily to audit API producers. And it has developed vendor assessment templates to streamline how manufacturers gather information on new suppliers. Supplier audits involve ensuring that these firms have their own security processes to prevent quality problems. The consortium tracks supply-chain policies and provides members with reports on the latest developments, but does not comment on specific rules or policies. A main goal is to identify and support opportunities for regional and international cooperation in addressing pharmaceutical supply chain threats.

—Jill Wechsler, Washington editor

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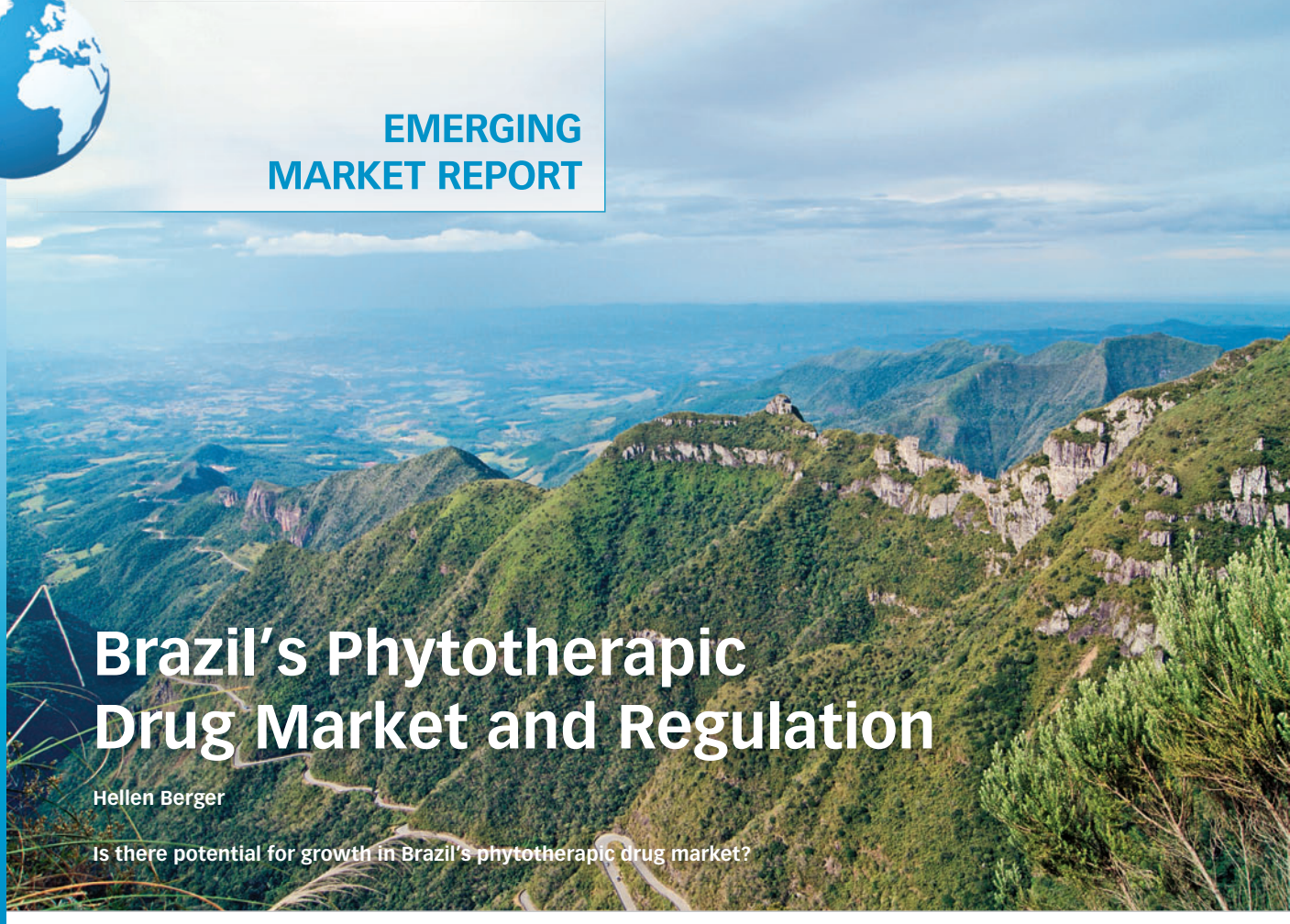

Brazil's Phytotherapic Drug Market and Regulation

Hellen Berger

Is there potential for growth in Brazil's phytotherapic drug market?

It is well known that Brazil has an immense biodiversity and that the Amazon is the largest tropical rainforest in the world. Traditional Brazilian medicines include African elements, rooted on indigenous groups. Few pharmaceutical companies, however, know at what level phytotherapic drugs are commercialized in the country, how much regulation is imposed for herbal medicines, and if there are any opportunities in this unspoken, mysterious market in Brazil.

Dozens of studies link Brazil's herbal medicines to successful treatments and cures of various ailments. According to Japanese scientists, there is strong anticancer activity in certain Brazilian traditional medicines (e.g., basic and applied studies for physiological activities of Brazilian traditional medicine). Another study analyzed antifungal properties of plants used in Brazilian traditional medicine against clinically relevant fungal pathogens. One more study made a comparison between ethnopharmacology in traditional Chinese medicine and Brazilian popular phytotherapy.

One would suppose that due to the potential of the market, there would be dozens of companies investing in the sector. This potential, however, is not translating into market growth, according to industry sources.

So why is the herbal drugs market in Brazil almost completely undiscovered and profoundly undeveloped? Is there any real potential for new or existing companies to enter this market?

There are few figures available on the local herbal drugs market, and its evolution is not officially followed, according to the Brazilian Health Surveillance Agency (Anvisa). It appears that most of the investment in the Brazilian herbal market has come from the cosmetics sector and not directly from the pharmaceutical industry.

A December 2011 study conducted by the University of São Paulo concluded that the number of patents filed at the Brazilian patent bank (76 patents) was much lower than that observed in its American (279) and European (328) counterparts and did not show clear signs of growth (1). The study was based on Brazilian, European, and American patent banks, with the objective of evaluating herbal extracts applied in cosmetics.

Alexandros Botsaris, president of the Brazilian Phytotherapy Association (Abfit), stated in an interview with *Pharmaceutical Technology* that there are various barriers in Brazil related to registration, environmental legislation, and local production of raw materials, which end up slowing down the availability of quality products in the local market. "Without a proper supply of products, no market is able to grow consistently," said Botsaris.

Anvisa has imposed regulation processes that include the registration of herbal medicines, according to Abfit.

"However, Anvisa was excessively strict regarding safety and efficacy criteria, which caused many smaller laboratories that produced traditional products to shut down," said Botsaris, adding that was the main reason why the volume of herbal drugs available in the local market reduced significantly in the past 15 years.

Botsaris adds that another issue is which products should be named "phytotherapic", as the term could include herbal extracts, 'in natura' products, or even items sold though network/pyramid marketing. "Brazil's herbal industry is in a very early stage if compared with other developed countries," says Botsaris. Brazil tends to follow guidelines published in the US, which could influence the Brazilian herbal market in the long term, he adds.

Also, according to Botsaris, environmental legislation made the use of Brazilian biodiversity extracts on commercialized products

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or research more complicated. "The CeGen (Cultural and Genetics Heritage Council) aggressively fined researchers and companies that invested in plants considered of Brazilian heritage, which has greatly inhibited the production of herbal medicines made with Brazilian plants," said Botsaris.

Legislation

According to Ana Cecília Carvalho, phytotherapic coordinator for the Brazilian Health Surveillance Agency (Anvisa), difficulties in the production of herbal remedies may arise due to legislation, which may not be changed by Anvisa. According to Carvalho, there are new norms being edited aiming at meeting other points not foreseen by the Brazilian Law to harmonize the legislation with international standards of quality, safety, and efficacy control.

"We hope these changes will make it possible for more herbal remedies to be available in the market and [guarantee] that every product will meet current international quality standards," Carvalho told *Pharmaceutical Technology*.

The local legislation for herbal drugs has evolved since 1967 in a few aspects to level itself a little more with international standards. In the past eight years, Brazil expanded its regulation principles regarding raw materials and created its good practice rules and other specific rules for herbal remedies to standardize the sector.

Since then, Anvisa updated and re-edited rules such as the *Guideline to Herbal Medicine Registration* (Director's Collegiate Resolution [RDC] 14/10) and the *Good Manufacturing Practices Guideline* (RDC 17/10), among others. "This is the fifth time the Herbal Medicine Registration is being re-edited ... the last version was RDC 14/2010," said Carvalho.

According to Carvalho, one of the main changes to the rules is related to the splitting of herbal products into two classes: one that passes all clinical studies needed for the new drugs registration to be granted and another for lower-risks products. "Lower-risk products do not need complete testing," she said, adding that the data from more than 30 years of usage on human beings is considered.

According to Carvalho, this makes approval of lower-risk herbal drugs a quicker process, with follow-up control by Anvisa itself. "The legislation update is needed in order to make sure that the consumer understands how the product purchased was registered ... if it was through standardized clinical trials or safe and effective usage, which is not clear today," said Carvalho.

To re-edit the rules, Anvisa analyzed various points of the international legislation from the World Health Organization (WHO), European Community, Canada, and Australia and extracted "the best" safety, efficacy, and quality principals from each, Carvalho said. According to Anvisa, various associations, scientists, and communities participated in the process.

Botsaris, however, states that Abfit was not happy with the process. "We have sent various suggestions to Anvisa and never had any idea actually used by them. We currently do not feel any type of proximity with the agency," he said.

"Abfit favors legislation and market systems similar to the ones found in Europe, where the government is active in validating traditional products, while there is also more flexibility for registration and prescription of [herbal] products," Botsaris added.

Growth and opportunities

Brazil's pharmaceutical market has grown in the past years as the volume of products available increased and new products emerged, especially those that were patent-protected, according to Abfit data. The association estimates, however, that the herbal drugs market has not followed the same trend. According to Abfit, the number of new registrations dropped by 50% at Anvisa in the past 14 years.

Anvisa also confirmed to *Pharmaceutical Technology* that there has been a reduction in the number of registered herbal drugs from manufacturers. "However, we have no means to offer [comparative] information on whether [the drop] was related with herbal drugs sales or financial values as Anvisa does not follow herbal drug sales and finances [/figures]," said Carvalho.

Despite the lack of statistics, it is possible to notice that the growth of herbal medicines in Brazil did not follow the evolution of the regular pharma market. On the other hand, according to Botsaris, Brazil historically follows international trends in this sector, and the search for natural drugs is increasing locally and worldwide so there are various good reasons to believe that the herbal industry in Brazil will offer great opportunities ahead and should receive more investments in the years to come.

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

Brazilian herbal-drugs market growth

Alexandros Botsaris, president of the Brazilian Phytotherapy Association, stated the following in an interview with PharmTech as reasons for growth in the Brazilian herbal drugs market:

- Brazil has a consistent and persistent market demand for natural, herbal remedies, especially aimed at treating simple health ailments or to promote wellbeing.
- Brazil possesses an enormous herbal biodiversity and the possibility of discovering various drugs and molecules with market potential as more investments are made in research and development.
- All needed resources are available such as workers, technology, farmland, and industrial complexes for establishing organized production chains.
- Brazil's natural drugs market offers limited availability of herbal products, while hundreds of herbal extracts with market potential are waiting to be discovered and launched.
- The recent regulation of the herbal-drugs market as well as the growth of phytotherapic health practices will generate prescriptions and increase demand for herbal medicines.

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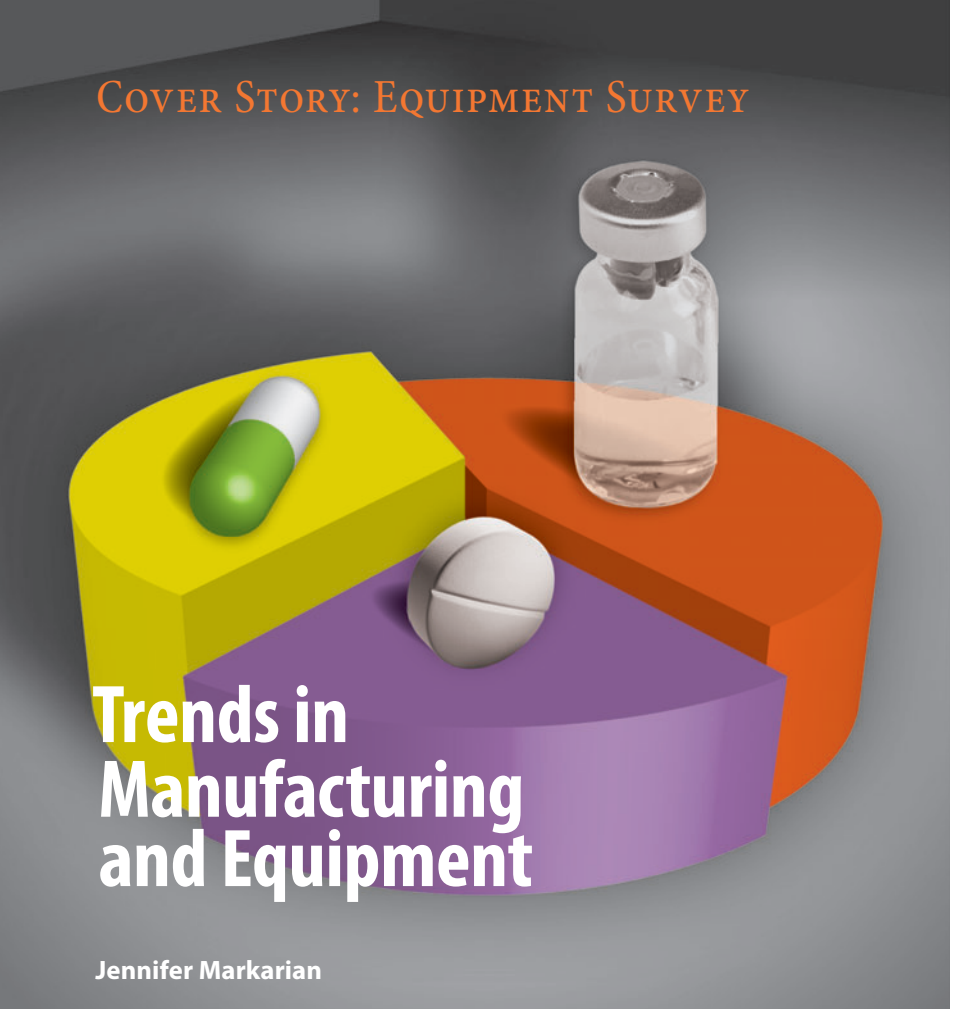


Trends in Manufacturing and Equipment

Jennifer Markarian

Pharmaceutical Technology's survey of finished drug-product manufacturing equipment and trends shows gains in process analytical technology and indicates areas for future innovation.

Pharmaceutical Technology's annual equipment and manufacturing survey collected industry feedback on trends and the utility of equipment used in finished drug-product manufacturing. Respondents to both solid-dosage and parenteral drug manufacturing questions indicated overall satisfaction with existing equipment and equipment innovation. Data indicated that process analytical technology (PAT) is growing in use, but some users also noted a need for improvement in existing PAT equipment and in new solutions. A majority of respondents continue to view quality-by-design (QbD) principles as important, and more than 90% of respondents have a positive view of metrics and trend analysis. Responses also indicated further growth in continuous manufacturing and in manufacturing of highly potent drugs. Other areas of innovation to watch include robotics and software.

Solid-dosage equipment

Existing solid-dosage equipment is generally meeting industry needs. Only one area—PAT/in-process testing—was indicated as poor or inadequate by more than one-third of respondents (see **Figure 1**). Nearly one quarter of respondents also indicated that innovation is lacking in this area. This dissatisfaction is up from 2013, in which 22% indicated existing equipment was poor or inadequate and 16% said innovation was poor (1). It is interesting to note that use of PAT also increased over the past year among those surveyed. Process control/automation and powder transfer/materials handling were also flagged as needing significant improvement in existing equipment (25% and 21% respectively) and in innovation (17% and 12%); these areas were also noted in 2013.

Respondents expressed greater confidence in the evolution of continuous solid-dosage manufacturing.

Continuous manufacturing. The percentage of respondents involved in solid-dosage manufacturing that use continuous processes either overall or in select unit operations was nearly 40%, which was similar to 2013. Respondents expressed greater confidence in the evolution of continuous solid-dosage manufacturing, with nearly 85% predicting that the technology would evolve to allow fully continuous processing; in 2013, only 67% predicted such development of the technology. Just over one-third of respondents, however, predicted that the industry would only apply continuous processing to select operations even if fully continuous processes are available. Several individuals commented that, although continuous processing would work for high volumes, they didn't see it being appropriate for small batch sizes. Half the respondents noted cost as a barrier to implementing continuous manufacturing, and over 40% also identified lack of expertise and insufficient PAT as barriers.

Parenteral equipment

The majority of parenteral-equipment respondents indicated that existing equipment is good or excellent, as shown in **Figure 2**. These respondents

Respondent's profiles

Pharmaceutical Technology's Equipment and Manufacturing Survey targeted individuals in production and engineering. The survey was conducted by email from February to May 2014 and had 254 respondents. Approximately 36% were from innovator pharmaceutical companies, 29% were from generic-drug companies, 18% were from contract manufacturers, and 9% were from consumer healthcare companies making over-the-counter products. The remaining respondents (less than 5% each) included excipient and raw material suppliers, equipment or machinery vendors, consultants, and members of universities. Approximately 60% of the respondents were involved with solid-dosage manufacturing and the other 40% in parenteral drug manufacturing. The majority of respondents (69%) were from companies with under $1 billion in revenue. More than 13% were from companies with between $1–10 billion in revenue, approximately 10% were from companies with $10–50 billion in revenue, and the remainder (8%) were from companies with over $50 billion in revenue.

also agreed that innovation is generally keeping pace with most, if not all, of their needs. Innovation was rated as excellent or good in lyophilization (95%), barrier isolation (91%), disposables (91%), vial and cartridge fill-finish equipment (92%), and prefilled-syringe fill-finish equipment (85%). Process control and automation was a weaker area, similar to 2013, with approximately 25% saying that existing equipment is either poor or inadequate, and 18% saying that innovation is poor.

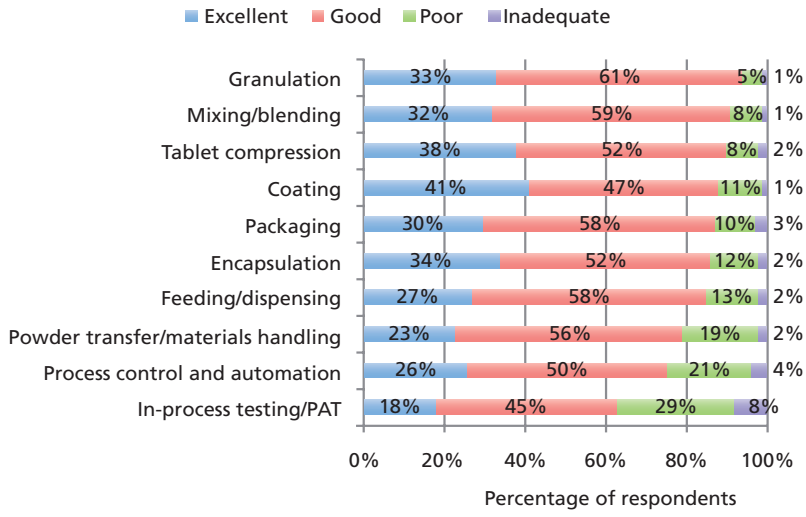
High-potency and high-containment

Just over one-third of respondents (in either solid-dosage or parenteral manufacturing) are involved with high-containment or high-potency manufacturing either in-house or at outsourced facilities. This percentage was up just slightly from last year's survey; however, in 2014, 78% indicated an increase in their company's level of activity over the past year up from 53% in 2013. When asked to identify the most challenging equipment or processing area, respondents' answers were diverse, with 21% each indicating system setup/changeover and getting materials into or out of the system during production. Other areas chosen as the biggest challenge included containment (17%), ergonomics (14%), air flow (10%), environmental issues (9%), and personnel protection (7%). Training and cleaning validation were also identified as challenges.

Equipment metrics

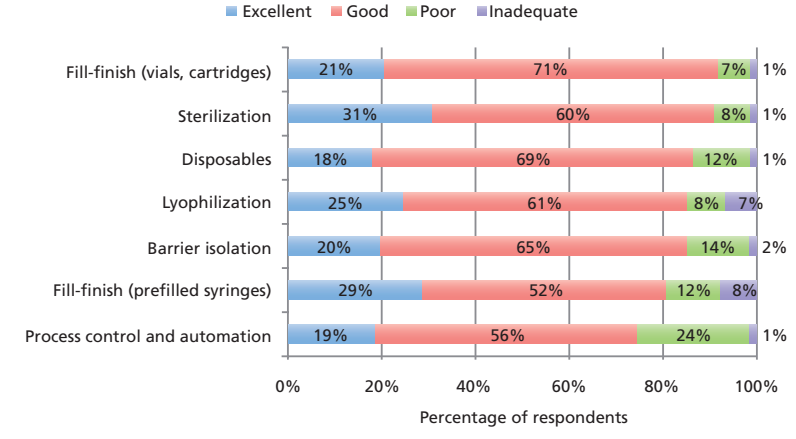
Those surveyed overwhelmingly agreed that metrics and trend analysis enhance the ability to improve equipment operation (92% of respondents). Actual use of metrics lagged this response somewhat. Approximately 75%

Figure 1: Utility of existing solid-dosage equipment.



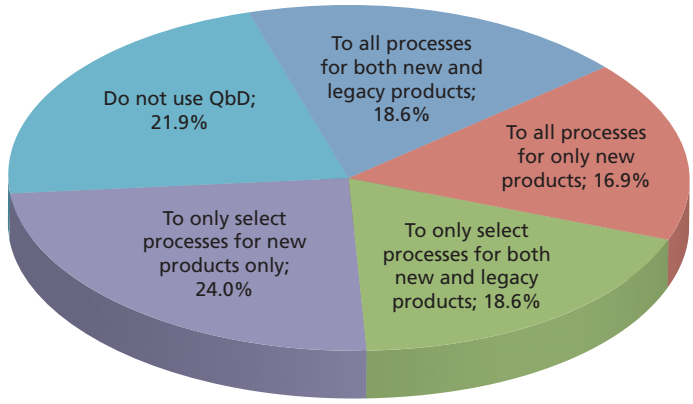
Percentages may not equal 100% due to rounding

Figure 2: Utility of existing parenteral equipment.



Percentages may not equal 100% due to rounding

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



stated that they use trend analysis to measure process or product deviations and relate this to equipment performance; 73% report that their company culture encourages optimizing manufacturing quality using metrics and trend analysis. Approximately 66% of respondents said their company has a metric(s) specifically to measure unplanned downtime of equipment (i.e., equipment failure).

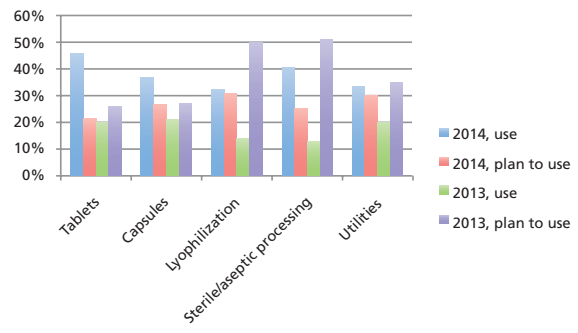
Use of process analytical technology increased significantly since 2013.

In both solid-dosage and parenteral areas, approximately half of respondents were aware of an equipment failure that had led to significant downtime or quality problems in the past year. When asked to identify the root cause(s), contamination or cleaning problems were most frequently chosen (44%), followed by utilities (37%), process validation (26%), nonconformance (25%), and other (11%) (multiple selections were allowed).

QbD

The majority of respondents use QbD principles in their manufacturing processes to some extent (see **Figure 3**). Approximately 35% apply QbD to all processes for new or all products, and nearly 43% apply QbD to select processes. Almost 22% indicated that they do not use QbD principles. Respondents noted several different challenges to implementing or barriers to using QbD (multiple answers allowed). The challenge most frequently identified was lack of knowledge or training (nearly 60% of respondents). Other challenges included lack of clarity in regulatory guidance (40%), management buy-in (38%), and availability of necessary equipment (35%) and software tools (31%). Nearly 10% said they saw no barriers or challenges.

Figure 4: Use of process analytical technology.



PAT

In the five manufacturing areas surveyed, the use of PAT increased significantly since 2013 (see **Figure 4**), with 32–46% of respondents in 2014 indicating that they currently use PAT compared to 13–21% of respondents in 2013 (1). The primary drivers for using PAT (multiple answers possible) include better process understanding (56%), increased efficiency (39%), reduced costs (34%), and shorter process times (30%). The use of PAT should continue to grow; between 20 and 30% of respondents in 2014 indicate plans to implement PAT in the coming year. Approximately one-third of respondents (33–37% depending on the application), however, do not currently use PAT and do not plan to implement it in the coming year.

Areas for innovation

Given these plans to implement PAT and the respondents who said that existing PAT tools do not meet their needs, as discussed previously, PAT is an area ripe for suppliers to develop new and improved instruments.

When asked about the most important area for innovation in pharmaceutical manufacturing, respondents mentioned some of the topics surveyed, such as continuous processing, QbD, and PAT, and several respondents listed automation. "Robotics are an inevitability," said one, and another commented, "Running 'lights out' [i.e., fully automated] would reduce the amount of hands-on time for production personnel." Related comments included calls for improved software to eliminate human error. A wide range of methods and technologies, including those evaluated in this survey, will play a role in the continued drive to improve product quality and process efficiency.

Reference

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Join the discussion

What do you see as the most important area for innovation in pharmaceutical manufacturing?

Post your comments on **www.pharmtech.com/linkedin**.

The Mainstreaming of Continuous Flow API Synthesis

Cynthia A. Challener

The pharma industry is moving toward commercial-scale continuous processes for small-molecule API manufacturing.

Continuous processing for the production of key building blocks and intermediates for small-molecule APIs is no longer viewed as a technology of the future. Most pharmaceutical companies with in-house manufacturing use flow chemistry to some extent, and smaller companies that outsource production expect their contract-manufacturing partners to have continuous-flow systems available. Advances in microreactor technology for commercial-scale production and implementation of continuous downstream processes will ultimately enable the complete continuous synthesis of complex organic molecules required for small-molecule API manufacturing. Widespread adoption, however, will occur slowly as the industry shifts from the infrastructure in place today to smaller, modular, and flexible facilities.

Many technical advantages

"Continuous flow synthesis is a great alternative to traditional batch synthesis/production when it comes to demanding chemistries such as hazardous reactions or potentially challenging conditions like high pressure and temperature," observes Dominique Roberge, head of continuous flow/microreactor technology business development at Lonza Custom Manufacturing. In addition, continuous flow processing provides many technical advantages over traditional batch methods, including speed of development, process reliability and product quality, maximization of process safety when employing hazardous chemistries, and minimization of investment during product development, according to Peter Poechlauer, principle scientist at DSM Fine Chemicals. For Jörg Schrickel, new business development manager for CABB, the more consistent quality that is achieved with continuous manufacturing, particularly for sensitive products, is of significance.

"There are, in fact, some products that cannot be produced in large batch processes due to the thermodynamic nature of the reactions involved. Under continuous flow conditions, however, because only small quantities of reagents and products are present at any given time, these issues can be avoided," Schrickel adds.

Another advantage is the improved environmental footprint of continuous processes. Poechlauer points to reduced raw material consumption and waste generation as two key benefits. CABB increases the sustainability of its continuous processes for the production of acid chlorides and derivatives by recycling off-gases (referred to by the company as its "verbund and recycling system"). "As a result, our building blocks have very low process mass intensity (PMI) and environmental factors (E-factors)," says Schrickel.

Slow but steady adoption

"Despite the obvious technical advantages of continuous flow processing, companies are adopting the technology steadily, but slowly, and in a strictly opportunistic way, applying elements of continuous processing technologies when they pay off immediately," states Poechlauer (1). "The technology is not developed to a certain degree of maturity and then waits to be applied, but is developed for and in close connection with a certain production process," he adds.

Flow chemistry is often considered as an option when exploring new chemical routes, increasing yield, lowering the cost of goods, and generating IP, according to Roberge. "One of the main drivers for the implementation of flow chemistry is, however, to perform a reaction that cannot be done with traditional batch production, such as those involving azide intermediates or oxidation using oxygen," he notes. Currently, the drivers for adoption are academia and institutes and providers of continuous flow equipment who are looking for innovation and often work together with the pharmaceutical industry to solve specific problems, according to Schrickel.

The main issue is the large existing batch manufacturing infrastructure. "If a company gets trapped in the ques-

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tion 'use existing or build new?', it will use the existing equipment in the present business environment," states Poechlauer. Continuous equipment like microreactors are added when needed, and the existing vessels modified to serve other purposes, such as hold-up tanks used to define the batch for regulatory purposes. "We expect most pharmaceutical syntheses will continue to be a mix of continuous and batch manufacturing operations, which also enables manufacturers to build in inventory buffer zones," observes Poechlauer.

to mid-size pharma and biotech companies often evaluate flow technology through outsourcing. "As a result, contract manufacturers that have flow processes in place are better positioned to engage in partnerships and collaboration discussions with these early start-ups," Roberge comments.

As the internal advocate groups within pharmaceutical companies push for the development of continuous processes, continuous processing will be applied in a growing number of processes, but in an evolutionary way, rather than a revolutionary one,

Flow chemistry is often considered as an option when exploring new chemical routes, increasing yield, and lowering the cost of goods.

In one recent example, researchers at GlaxoSmithKline found that for the large-scale manufacture of potassium bromomethyltrifluoroborate, a key raw material for a Suzuki–Miyaura coupling reaction (2), a hybrid approach involving the use of both continuous and batch processing where most appropriate was successful in achieving the project goals, according to Toby Broom, a chemist with GlaxoSmithKline R&D.

Current perspective

"The pharmaceutical industry is very much interested in continuous processes, and a lot of activity is underway within most pharmaceutical companies related to the development of continuous processes. However, we do see continuous processes being more relevant for the next generation of APIs," says Schrickel. Lonza believes that at least the top 20 pharmaceutical companies have flow systems within their assets at this point in time, with some of the larger players calling continuous processing a disruptive or breakthrough technology, according to Roberge. At the same time, small as people come to accept the technology as mainstream rather than "experts only" territory, according to Poechlauer. In addition, he notes that with large pharmaceutical houses focusing on new leads rather than on process development, custom manufacturing organizations continue to play an important role in this field.

Support from the authorities for continuous processing has also been crucial in furthering its acceptance by small-molecule API manufacturers. "The industry and FDA are in constant dialogue on continuous processing," Poechlauer says.

Advances in continuous commercial production

One of the biggest issues for continuous flow chemistry has been scaling up to commercial production levels, because most early equipment for flow chemistry was designed for the laboratory. According to Poechlauer, however, chemical manufacturers and pharmaceutical companies have been working with microreactor manufacturers to address this issue, and pilot- and small commercial-scale

equipment is now available, often by "numbering up" and running several microreactors in parallel. "One advantage of this approach is that modular designs that can be fitted to the specific needs of different reactions are possible," he says.

This advantage was taken into consideration when DSM installed its commercial-scale microreactor suite.

cessing of liquid/solid and multi-phase systems," he explains. Lonza, for example, is developing microreactor plates with its partner Ehrfeld Mikrotechnik BTS, a Bayer Technology Services company, that will enable multi-phase reactions. Schrickel believes these advances will be important for the further application of continuous processes in API production.

Advances have been achieved in expanding flow chemistry beyond liquid systems.

"We are very interested in microreactor technology and continuous processing because, in some cases, it makes it easy to scale up reactions that can't easily be done otherwise due to the nature of the raw materials or the kinetics of the reaction," says Poechlauer.

Lonza has designed a new type of production facility concept called the "Factory of Tomorrow" in which FlowPlate microreactors of various sizes are incorporated into the company's development and manufacturing plants. "Flow processes lead to high intensification that radically reduces the size of a reactor and its footprint," Roberge states. The range of FlowPlate equipment allows for production of a few grams of product in the lab setting and up to 5-ton campaigns for later-stage projects. "In such an environment, flexibility and versatility is needed to combine novel process conditions at high temperature and pressure, which can be difficult to achieve in a classical plant setting. Continuous manufacturing can significantly improve process efficiency with a reduced footprint, therefore reducing overall material consumption," he observes.

In addition to addressing scale-up issues, advances have also been achieved in expanding flow chemistry beyond liquid systems, which are the traditional and most simple systems for continuous processing, according to Schrickel. "Much progress has been made with respect to the development of technology for the continuous pro-

Poechlauer does add that there are uncertainties about scale-up, and managing intellectual property issues must be done carefully, given that in many cases new process chemistry is involved.

Flowing downstream

More recently the focus has been on integrating continuous downstream processes with continuous flow synthesis. "Most downstream processes can be easily adapted to run continuously; extractions, phase separations, and distillations are actually more effective when done continuously," says Poechlauer. On the other hand, he notes that solids handling processes, such as filtration and crystallization, present some difficulties. There are solutions being introduced to the market, however, such as belt filters and spray-drying, and Poechlauer expects others will follow.

Lonza, in fact, is currently extending the application of continuous flow technology to address continuous work-up unit operations such as distillation, according to Roberge. "The objective is the continuous operation of a complete mini-plant within the manufacturing unit 'Factory of Tomorrow,' which will allow its use for larger-scale manufacture," explains Roberge.

Intense future

Research and development of continuous processes will continue and grow, first on specific, isolated topics, because there might not always be a solution that will enable a complete continuous process or at least a process without bottlenecks. To switch to continuous processes, companies will have to gain all of the possible benefits that the technology offers, and sustainability will be one of the key aspects, asserts Schrickel.

Poechlauer also believes that continuous processes will ultimately lead to simplified distributed manufacturing (on-site, on-demand) in modular container plants as well as enable application of "personalized medicines." He also notes that the use of disposable devices in the manufacture of highly potent compounds will be beneficial to the further development of continuous processes for these challenging compounds.

"Our partners in the pharmaceutical industry are in a transition stage and are moving toward integrated solutions. Laboratory chemists consider the environmental consequences of raw materials and processes when developing synthetic routes. Drug manufacturers are also forming closer collaborations with suppliers to explore new technologies and concepts, such as continuous processing and the use of microreactors. Such relationships will help demonstrate the benefits of this approach and ultimately lead to adoption of process intensification when it is the most effective solution," Poechlauer concludes.

At the same time, continuous processes will require new equipment and perhaps dedicated production lines for each API, according to Schrickel. "Pharmaceutical companies may insource the entire manufacturing of their APIs or force their outsourcing partners to install dedicated continuous plants. In either case, the adoption of continuous processes may result in a radical change in the pharmaceutical and outsourcing industry," he asserts.

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Cleanability of Pharmaceutical Soils from Different Materials of Construction

Richard J. Forsyth, Keith Bader, and Kelly Jordan

The ability to remove soils from manufacturing equipment is the basis of cleaning validation. Pharmaceutical soils vary from simple excipients, buffers, and salts to complex pharmaceutical formulations. Cleanability measurements establish the relative degree of difficulty in removing the soils from the manufacturing equipment surfaces and provide necessary data to more accurately define a worst-case soil for cleaning validation. The authors look at the cleanability of pharmaceutical soils from a variety of materials of construction to determine the relative ease of cleaning and explore potential grouping strategies as part of a comprehensive cleaning validation program.

A cleaning procedure is expected to remove soil from product-contact equipment surfaces. A validated cleaning procedure has been shown to reliably remove soils from these surfaces. One of the accepted approaches to cleaning validation is to identify a worst-case soil for validation. A worst-case soil is one that is the most difficult to clean in relation to all other soils manufactured in a pharmaceutical facility. If the worst-case soil can be cleaned to an acceptable level, it can be concluded that the other soils in the facility can also be cleaned to an acceptable level using the validated cleaning procedure.

Identification of a worst-case soil can be accomplished through equipment-washer and formulator experience. Those involved in manufacturing formulations, cleaning, and maintaining the equipment are in the best position to identify the hardest-to-clean soil. This approach is a practical but subjective determination and would leave a facility open to question until ongoing data supports the initial conclusions on the worst-case soil.

A second approach is a comparison of API solubility. Solubility data for APIs are typically generated in water and organic solvents as part of the physical and chemical characterization workup for the API. Those APIs that are least soluble in the cleaning solvent are considered the hardest to clean. This approach neglects the formulation excipients, which are often insoluble, comprise a much greater percentage of the formulation, and can be more difficult to clean than the API.

A more empirical method to determine a worst-case soil is to spot coupons with the soils, allow them to dry, and clean them using the identical conditions encountered in the cleaning cycle. Equipment surfaces, however, encounter different types of cleaning action depending on their location in the manufacturing equipment. Soils could be subjected to manual scrubbing, impingement under the cleaning solvent, turbulent flow from a pump forcing cleaning solvent through piping, or a cascade action as the cleaning solvent moves across equipment surfaces.

Cleanability studies are typically conducted using dried residue spotted on a coupon dipped into a beaker containing water or the cleaning solvent or solution. The cleaning solvent is stirred, creating a less rigorous cleaning action than encountered during actual cleaning, and would be considered a worse-case condition. The experiment can be

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Submitted: March 1, 2013. Accepted: April 16, 2013.

conducted at room temperature or an elevated temperature. The soil with the longest cleanability time can be considered the worst-case soil for cleaning validation within the variability of the test parameters. Numerous studies have been conducted to demonstrate cleanability. Studies range from a paper-based evaluation of a facility's soils (1) to basic laboratory conditions, such as suspending the coupons in a beaker of cleaning solvent, all the way up to a sophisticated cleanability bath (2). Cleaning parameter variations have been characterized using cleaning process design on bench-scale studies (3), but for this study the cleaning parameters were held constant. Statistical equivalence testing for assessing cleanability (4) can show that soils are cleaned to an equivalent extent. If potential worst-case soils demonstrate comparable cleanability, it would be prudent to use more than one worst-case soil for further testing.

A well-executed cleanability study is one part of a comprehensive cleaning validation program. The experimental cleanability can be preceded by an evaluation of the formulation components to narrow the number of soils tested. The selected soils and materials of construction can be tested using a matrix approach to determine a worst-case soil and a hardest-to-clean material of construction.

Complementary studies can include—rinse recoveries and swab recoveries for analytical testing, and visible residue limits (5) for inspection of cleaned equipment. The studies can be conducted in parallel, often using the same coupon samples for multiple studies. All studies might not be necessary, based on the number of formulation soils and the manufacturing equipment involved, but a comprehensive picture of the physical properties of the soils during cleaning, and the ability to test and detect residual soils after cleaning, form a sound basis for a validated cleaning program.

Table I. Material-of-construction coupon types.

316 stainless steel
Glass
Polypropylene
Acrylic
Polytetrafluoroethylene (Teflon)
Silicone
Synthetic fluoropolymer rubber (Viton)
Nickel-steel alloy (Hastelloy)
Ethylene propylene diene monomer (EPDM)
Polyether ether ketone (PEEK)

Methods

The cleanability study was conducted to determine ease of cleaning for a variety of soils on a range of material-of-construction coupons using the following param-

Table II. Time to visual cleanliness (min).

Materials of construction	Growth media 10% serum - A	Regeneration buffer	Zinc buffer	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	7:18	0:09	0:10	4:09	3:11	5:43
Acrylic	4:33	N/A	N/A	5:49	0:58	4:20
Ethylene propylene diene monomer (EPDM)	0:46	N/A	N/A	0:32	0:13	0:39
Glass	5:33	N/A	N/A	0:22	0:10	7:16
Nickel-steel alloy (Hastelloy)	6:22	N/A	N/A	6:17	1:19	4:37
Polyether ether ketone (PEEK)	0:28	N/A	N/A	0:22	0:20	4:17
Polypropylene	3:17	N/A	N/A	0:25	0:17	1:16
Silicone	0:28	N/A	N/A	0:29	0:32	0:33
Polytetrafluoroethylene (Teflon)	0:33	N/A	N/A	0:35	0:11	0:40
Synthetic fluoropolymer rubber (Viton)	0:25	N/A	N/A	0:22	0:10	0:26

N/A – these two soils did not dry. Times on stainless steel are representative of all material-of-construction coupons.

eters. **Table I** lists 10 material-of-construction coupon types, which are among the commonly used materials of construction in pharmaceutical and biopharmaceutical manufacturing. All 10 materials of construction were tested during the study.

The cleanability study to determine the worst-case soils was conducted using three buffers and three media under the following parameters. The coupons were weighed and soils were spotted in triplicate for each of the material-of-construction coupon types listed in **Table I**. Each individual coupon was spotted with 1 ml of the soil. The soil was allowed to dry for at least 4 hours, or until visually dry, but no longer than 3 days, which was the established dirty hold time. Following drying, the coupons were reweighed and the coupon weight was subtracted to determine the weight of the residue. The coupons were immersed in a 600-ml beaker containing 400 ml of room-temperature purified water. The 600-ml beaker was the smallest beaker that would hold the 2.5" x 2.5" coupons without impeding flow around the coupons during testing and 400 ml was the minimal volume necessary to completely cover the coupons. The water was agitated on a magnetic stirrer at a fixed rotation and did not generate a vortex during testing. The cleanability endpoint was defined as the time at which the soil was no longer visible to the observer under defined conditions: distance 18 inches, optimal viewing angle dependent on the material-of-construction coupon type, and 700 lux light intensity. The coupons were removed from the beaker immediately after the visual endpoint was determined.

The visual endpoint was confirmed analytically through conductivity, total organic carbon (TOC), and gravimetric testing. The cleaning solution in the beaker was tested for conductivity. A sample of the cleaning solution was taken and tested for TOC. Positive controls were tested for conductivity and TOC by pipetting 1 ml of soil directly into a beaker and testing for conductivity and TOC. After drying, the coupons were again weighed and the weight was compared to the initial weight to determine cleanability of the soils gravimetrically.

Results and discussion

The material-of-construction coupons chosen for the study were seen as representative of a wide variety of materials. A number of liquid soils were chosen to represent a sampling of pharmaceutical and biopharmaceutical soils. Implementation of this approach at a site should address all soils on all materials of construction employed at the site unless an abbreviated approach can be justified.

Instruments were checked with every use to ensure they were operating properly and within calibration dating. The soils and the cleanability results along with supporting TOC and conductivity data are presented in the following sections.

Two buffers (regeneration buffer and zinc wash buffer) were spotted and held for 3 days to match the proposed dirty hold time maximum, but these buffers did not dry due to high ethylene glycol content. It should be noted that a properly executed paper-based evaluation (1) would have eliminated these two soils from the laboratory testing and saved 2 days of waiting for each of the trials. The assays for these two buffers on 316-finish stainless steel were representative for all of the materials of construction.

The visual removal data generated for the soils as shown in **Table II** demonstrated complete removal of the soils from all materials of construction. The data in **Tables II–V** are expressed as an average of the three individual determinations. Times vary widely, with the two buffers that did not dry rinsing from all coupons within 10 seconds. The 316-finish stainless steel and nickel-steel alloy (Hastelloy) coupons were the only materials of construction that demonstrated retention of the other four soils. They provided a representative ranking of the cleanability for all the soils and comprised the vast majority of material-of-construction surface area for all automated cleaning circuits. Ethylene propylene diene monomer (EPDM), silicone, polytetrafluoroethylene (Teflon), and synthetic fluoropolymer rubber (Viton) all became visually clean quickly for all soils, making any type of soil ranking difficult on those materials. Of the remaining four material-of-contruction coupon types: acrylic, glass, polypropylene, and polyether ether ketone (PEEK), all retained some soils but not others. These inconsistent results were coupled with the fact the soils retained by these materials were also retained strongly by 316-finish stainless steel and nickel-steel alloy (Hastelloy). Visual endpoint testing is subjective, and therefore, should be done in multiples by a small, well-trained personnel group to maintain consistency for the observations.

The conductivity results shown in **Table III** demonstrated high percentage of removal from all of the materials of contruction for each of the soils except for the regeneration buffer with 20% ethanol, which evaporated during the coupon drying. Removals greater than 100% can be attributed to day-to-day variance in calibration of the conductivity meter. Conductivity, however, could be misleading. The conductivity readings began to plateau well before the coupons became visually clean. The conductivity levels of the fully dissolved soils were relatively low (<60 µS/cm). Use of conductivity measurements should confirm the conductivity of the soils and should graph the rate of soil removal during cleanability testing and compared to visual endpoint measurements.

The gravimetric results in **Table IV** show complete removal of the residues. Other than 316-finish stainless steel, glass, and nickel-steel alloy (Hastelloy), the material-of-construction coupon types demonstrated some results where the final weight was less than the initial weight, indicating that the coupons continued drying over a number of days at ambient temperature. This observation makes all other materials of construction poor candidates for the initial cleanability unless they are oven dried and could affect the speed and accuracy of a study. Continued use of gravimetric measurements for the 316-finish stainless steel and glass coupons would provide data of limited

Table III. Conductivity results (% removed).

Materials of construction	Growth media 10% serum - A	Regeneration buffer	Zinc buffer	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	97%	49%	97%	97%	102%	94%
Acrylic	117%	N/A	N/A	98%	101%	95%
Ethylene propylene diene monomer (EPDM)	115%	N/A	N/A	95%	99%	94%
Glass	118%	N/A	N/A	95%	103%	94%
Nickel-steel alloy (Hastelloy)	90%	N/A	N/A	110%	114%	99%
Polyether ether ketone (PEEK)	89%	N/A	N/A	108%	114%	97%
Polypropylene	118%	N/A	N/A	97%	102%	95%
Silicone	86%	N/A	N/A	110%	113%	100%
Polytetrafluoroethylene (Teflon)	119%	N/A	N/A	97%	103%	94%
Synthetic fluoropolymer rubber (Viton)	114%	N/A	N/A	97%	101%	94%
Positive Control Data						
Conductivity (µS/cm)	47	56	42	40	46	45

N/A – these two soils did not dry. Conductivity data on stainless steel are representative of all material-of-construction coupons.

Table IV. Gravimetric results (% removed).

Materials of construction	Growth media 10% serum - A	Regeneration buffer	Zinc buffer	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	99%	100%	100%	100%	96%	99%
Acrylic	100%	N/A	N/A	100%	100%	100%
Ethylene propylene diene monomer (EPDM)	100%	N/A	N/A	100%	100%	100%
Glass	99%	N/A	N/A	99%	96%	100%
Nickel-steel alloy (Hastelloy)	99%	N/A	N/A	100%	100%	99%
Polyether ether ketone (PEEK)	100%	N/A	N/A	99%	81%	94%
Polypropylene	100%	N/A	N/A	100%	100%	100%
Silicone	100%	N/A	N/A	100%	100%	100%
Polytetrafluoroethylene (Teflon)	100%	N/A	N/A	99%	99%	100%
Synthetic fluoropolymer rubber (Viton)	100%	N/A	N/A	100%	100%	100%

N/A – these two soils did not dry. Percent on stainless steel is representative of all material-of-construction coupons.

value, given that gravimetric testing demonstrated complete soil removal but did not provide an endpoint determination. Other testing is necessary in conjunction with gravimetric determinations.

TOC testing results, as shown in **Table V**, were reasonably consistent with the conductivity and gravimetric. One soil, phosphate buffered saline, had no organic carbon to measure and was, therefore, not applicable for this test. The results for the first media were consistently high, as were the conductivity results. The most likely cause would be a low positive control, but because the gravimetric results were consistently good, a repeat of the experiment was not necessary. Most soils required multiple dilutions prior to TOC testing, and testing was time-consuming compared

Table V. Total organic carbon (TOC) results (% removed).

Materials of construction	Growth media 10% serum - A	Regeneration buffer	Zinc buffer	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	116%	80%**	89%	83%	*	88%
Acrylic	113%	N/A	N/A	83%	*	88%
Ethylene propylene diene monomer (EPDM)	113%	N/A	N/A	83%	*	89%
Glass	117%	N/A	N/A	82%	*	89%
Hastalloy	***	N/A	N/A	***	*	***
polyether ether ketone (PEEK)	***	N/A	N/A	***	*	***
Polypropylene	117%	N/A	N/A	83%	*	90%
Silicone	***	N/A	N/A	***	*	
Polytetrafluoroethylene (Teflon)	115%	N/A	N/A	94%	*	89%
Synthetic fluoropolymer rubber (Viton)	113%	N/A	N/A	82%	*	89%
Positive Control Data						
TOC (ppm)	10120	125440	120640	7440	*	11184

N/A – these two soils did not dry. TOC data on stainless steel are representative of all MOC coupons.
* Phosphate buffered saline contains no TOC.
** Soil contained 20% ethanol, which evaporated during drying.
*** Data not generated. Samples expired due to instrument malfunction.

to conductivity and gravimetric testing making TOC a less attractive soil removal confirmation test.

The evaluation of the data to identify the worst-case soil on the hardest-to-clean material of construction should be done in tandem. **Table VI** ranks the four retained soils on each material of construction from 1 to 4, with 1 being the hardest to clean. The rankings were then averaged across the soils and Media A was determined to be the hardest to clean soil by a small margin over the media with phenol red.

Table VII ranks retention on the six out of 10 materials of construction that demonstrated retention characteristics. The four soils were ranked from 1 to 6, with 1 being the hardest-to-clean material of construction. The rankings were then averaged across the materials of construction and 316-finish stainless steel and nickel-steel alloy (Hastelloy) were determined to be the hardest-to-clean materials of construction by a wide margin.

Table VI. Worst-case (hardest to clean is ranked as 1) soil versus material of construction.

Materials of construction	Growth media 10% serum - A	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	1	4	3	2
Acrylic	2	1	4	3
Glass	2	3	4	1
Hastalloy	1	2	4	3
Polyether ether ketone (PEEK)	2	3	4	1
Polypropylene	1	3	4	2
Average ranking (Sum/6)	1.5	2.7	3.8	2.0

Table VII. Worst-case (hardest to clean is ranked as 1) material of construction versus soil.

Materials of construction	Growth media 10% serum - A	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red	Average ranking (Sum/4)
316 stainless steel	1	3	1	2	2.0
Acrylic	4	2	3	4	3.25
Glass	3	4	6	1	3.5
Hastalloy	2	1	2	3	2.0
Polyether ether ketone (PEEK)	6	6	4	5	5.25
Polypropylene	5	5	5	6	5.25

The worst-case combination of soil and material of construction was Media A on 316-finish stainless steel or nickel-steel alloy (Hastelloy) for the soils and materials of construction tested. The soil and material-of-construction matrix at a facility can be combined into groups based on data and identification of a worst case. A similar analysis for swab recoveries (6, 7) identified stainless steel as a representative material of construction for most equipment and for a large majority of soils. The present study indicates a similar conclusion, (i.e., 316-finish stainless steel is a representative material of construction for cleanability), but the data set is too small to be conclusive. This type of grouping strategy should be explored for each facility to streamline experimentation while still presenting a comprehensive picture of the soils and materials of construction in manufacturing operations.

Cleanability testing of the matrix of soils and materials of construction at a given site can cover all soils on all materials of construction or can be focused based on an evaluation of the components of the soils (1), coupled with preliminary testing over the range of materials of construction. The testing plan should be done within the overall cleaning evaluation including cleaning cycle development, swab and rinse recoveries, and visible residue limit determinations.

Conclusion

Cleanability studies can provide objective data on the hardest-to-clean soil at a facility. Conclusions could differ based on the soils and materials of construction at a given facility. A similar survey of soils and materials of construction should, therefore, be executed. Measuring the cleanability endpoint should be done consistently, including visual observation and at least one other confirmation test. The resulting cleanability data can vary for different materials of construction depending on the soil, and an evaluation of the matrix of soils and materials of construction will provide a path forward for cleaning validation execution.

For this study, based on the materials of construction and soils tested, it can be concluded that performing cleaning validation of the worst-case soils focusing on the 316-finish stainless steel or nickel-steel alloy (Hastelloy) surfaces with conductivity results to confirm visual results is an approach that will provide the most conclusive results. These materials have the added advantage of being the most frequently used materials of construction for all automated cleaning circuits.

Although important, cleanability is only one aspect of a comprehensive cleaning validation program. Personnel cleaning experience, rinse recoveries, swab recoveries, visual residue limits, cleaning cycle development, and cleaning validation are all crucial elements of a well-defined, documented, and defendable cleaning program.

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Overcome Softgel Coating Challenges

| ON-DEMAND WEBCAST

Register for free at www.pharmtech.com/coating

EVENT OVERVIEW:

Soft gelatin capsules (softgels) have become an increasingly popular method for the delivery of pharmaceuticals and dietary supplements due to to the ability to encapsulate sensitive compounds, accurately deliver potent molecules, and directly appeal to the consumer. However, applying a functional coating to softgels is a challenging endeavor requiring precise formulation and finely tuned processing parameters that only recently have been explored. In this webcast, pharmaceutical scientists and formulators will learn about key aspects of successful softgel coating processes.

Discussion topics include:

- An introduction to softgels and their increasing role in pharma
- Key challenges for the coating of softgels
- Case study examples of softgel coating utilizing different functional polymers
- Typical problems and solutions encountered in coating of softgels
- Creating added patient value through functional softgel coatings

Key Learning Objectives:

- Understand the fundamental characteristics and advantages of softgels
- Build awareness of the key factors that define the quality of a softgel coating
- Develop knowledge to improve suboptimal softgel coatings

Presenters

KAI ZHUANG
Senior Technical Sales Representative,
Pharma Ingredients and Services
BASF

FRANK ROMANSKI
Scientist,
Pharma Ingredients and Services
BASF

Moderator

RITA PETERS
Editorial Director
Pharmaceutical Technology

Who Should Attend:

This webcast targets all pharmaceutical scientists and formulators that have an interest in the production of softgel capsules. In addition, this webcast will seek to highlight new opportunities for pharmaceutical marketing professionals on creating added patient value through functional softgel coatings.

Presented by

Pharmaceutical Technology

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BASF
The Chemical Company

Added Value:
Attendees of this webcast will recieve a FREE Whitepaper

For questions, contact Sara Barschdorf at sbarschdorf@advanstar.com

Automating Online Sampling of Bioprocesses

DANLEAP/GETTY IMAGES

PharmTech.com/Troubleshooting

Cynthia A. Challener

The Modular Automated Sampling Technology platform allows sampling of bioreactors.

Unlike in the chemical and food industries, and even in small-molecule pharmaceutical manufacturing, which have well-established methods for automated online sampling, the biopharmaceutical sector remains in need of a reliable system that transfers bioprocess samples directly from bioreactors to analytical devices while maintaining process sterility. Such a system is necessary if biopharmaceutical companies are to effectively take advantage of process analytical technology (PAT) and gain a more fundamental understanding of what is happening within bioreactors. While on-line Raman and dielectric spectroscopy provide some insight, there remains a need for integration of this data with off-line measurements, such as cell density, viability, metabolite levels, and titers.

To overcome this issue, Bend Research (part of Capsugel Dosage Form Solutions), in collaboration with major biopharmaceutical companies, including Pfizer, Eli Lilly, and Boehringer Ingelheim, has developed the Modular Automated Sampling Technology (MAST) platform. MAST consists of a sterile sampling system, a sample scheduler and navigator for automated sampling and delivery of samples to various analytical instruments, and a data-management system for collecting and analyzing the results, and if desired, providing feedback to the bioreactor for direct adjustment of reaction conditions.

Sterile sampling

The heart of the MAST platform is the new sterile sampling unit referred to as the Sample Pilot, which consists of a sampling module and an associated programmable logic controller (PLC). There are two Sample Pilot modules, the SP100, which collects 50-mL samples for monitoring of pilot- and commercial-scale manufacturing operations, and the SP200, which takes incremental 5-mL samples for analysis of development-scale reactions and reactions that run in smaller laboratory-scale bioreactors and pilot-scale, single-use bioreactors. Each sample assembly consists of proprietary valves and a pump and is designed to draw samples from the bioreactor and push them out to user-defined destinations, according to Clint Pepper, a director at Bend Research. "Because we use positive displacement, rather than pulling the samples out with a vacuum, it is possible to deliver even viscous culture samples with high cell densities to analytical instruments more than 50 feet away."

Importantly, both systems can be sterilized in place (SIP), autoclave-sterilized, or gamma-sterilized depending on the model selected. "The entire system can be cleaned and sanitized between each sampling, and there is flexibility for users to adapt various cleaning procedures depending on their specific needs," notes Lisa Graham, senior vice-president of Bend Research.

Sample and data management

To maximize the potential of sterile biopharmaceutical sampling, the MAST platform design includes software systems for managing sample scheduling, delivery of the samples, processing of the analytical results, and adjustment of bioreactor parameters if desired. The MAST Sample Scheduler and Navigator modules will work together to facilitate sample collection from bioreactors and transfer to analytical testing systems.

The MAST Data Management system will maintain information on sampling activities and analysis results and has the ability to automatically adjust the feed rate of the bioreactor to meet desired growth rates according to the current condition of the cells. "With this data management system, it is possible to significantly reduce the time needed to process large sets of analytical results. Information on the state of cells and the process is obtained more rapidly, " Pepper asserts.

On-line measurement combined with at-line analysis

Early studies at Pfizer have shown that automated at-line measurements obtained using the MAST system are similar to those obtained when using manual samples. The MAST platform has been incorporated with on-line analytical technologies to deliver overall cell-level "observability" and "guidance," according to Graham. In one case, dielectric spectroscopy measurements were corrected to more accurately estimate total and viable cell density. Off-line measurements of Caspase-3 activation were related to on-line measurements of the variation in the capacitance due to the reduction in cell viability following staurosporine addition. This information was used to determine cell health in the bioreactor in real time. In another example, the amount of off-line data that was collected (Raman spectroscopy) was greatly increased due to the ability to more frequently collect samples automatically and without the need for an operator. The data were used to build robust process-monitoring models and develop a Raman system for laboratory use, according to Graham. "In this case," she observes, "the Sample Pilot serves as enabling technology for the implementation of PAT."

Cynthia A. Challener, PhD is a contributing editor to *Pharmaceutical Technology.*

Demonstrated performance

The steam-sterilized SP100 module has been successfully demonstrated in five different bioreactors in three different facilities. "During recent development runs on pilot-scale bioreactors, the MAST platform and SP100 successfully delivered more than 480 samples without contamination, including more than 200 cumulative days of successful operation at the 30-L to 500-L scales in both cell culture and microbial applications," reports Pepper. "The sanitant-sterilized SP200 module has been deployed in five different facilities ranging in scale from bench reactors to large-scale, single-use bioreactors. The SP200 units have collected over 2000 samples in more than 240 accumulative days of operation with no contamination or loss of sample integrity."

MAST systems have been placed in nine client facilities (15 total units installed) with more than 2400 sterile samples collected without loss of sterility. "The major MAST product modules have moved out of the beta testing stage and are being sold to early adopters as pre-commercial products," says Pepper.

Next enhancements

New MAST technologies are still being beta tested, including a module to automatically remove cell from the whole broth, leaving the clear supernatant. This module would send clear samples to analytical devices that require cell-free samples, such as liquid chromatographs and mass spectrometers, so that these instruments can be integrated for real-time data collection and processing.

In the near future, Bend Research plans to install the first multiplexed MAST system capable of collecting samples from up to eight bioreactors and sending those samples to as many as four analytical devices. "This solution should gain a lot of traction in the laboratory setting where banks of bioreactors are running at the same time," says Pepper.

Enabling process control

The MAST platform offers the ability to collect reproducible samples more frequently and automatically without operator involvement, which reduces the risk of contamination and operator exposure. The ability to integrate analytical results from numerous sources provides more insight into cell behavior and the impact of process parameters, enabling the use of more sophisticated process-control strategies.

"Our intention with the MAST platform is to help biopharmaceutical companies gain insight into what actually occurs in a bioreactor by providing a means for understanding how bioprocess variables affect overall product quality," comments Graham. "We believe that by coupling the right tools, the MAST platform provides in-depth guidance for optimization of the reactor environment in order to meet cell needs for the production of the target product. Ultimately, we hope that the MAST platform will provide the meaningful real-time analytics, process measurements, and novel data management techniques that will enable the development of predictive control models that in turn will drive increased product consistency and batch-to-batch reproducibility," she concludes. **PT**

The Sample Pilot SP200 shown here in a typical installation.

IMAGE COURTESY OF BEND RESEARCH

DANLEAP/GETTY IMAGES

Multifactor Non-linear Modeling for Accelerated Stability Analysis and Prediction

Mark Alasandro and Thomas A. Little

The right approach can provide a clear, statistically defendable method for determining dissolution and accelerated stability.

Accelerated stability analysis is a strategy used to quickly evaluate alternative formulations, packaging, and processes. Accelerated linear studies are commonly performed and modeled; however, accelerated multiple-factor non-linear modeling has been a gap, and statistical software tools such as SAS/JMP do not directly have any provision to model multiple factor nonlinear responses. This paper outlines an approach to model and predict non-linear multiple factor stability/tablet dissolution data under accelerated and nominal storage conditions.

There are many non-linear stability cases such as dissolution, leachables, and moisture. Being able to model these non-linear processes is crucial to proper drug development. In addition to general non-linear modeling, there are multiple factors that may influence the non-linear curve. The following is a list of factors that may impact the asymptotes, growth rate, and inflection point of a curve:

- Stability storage temperature and humidity
- Particle size
- pH
- Amount of an excipient
- Processing conditions and/or set points
- Packaging materials/method

Mark Alasandro, PhD, is director, Allergan Irvine. **Thomas A. Little PhD**, is president, Thomas A. Little Consulting, drlittle@dr-tom.com.

Study design

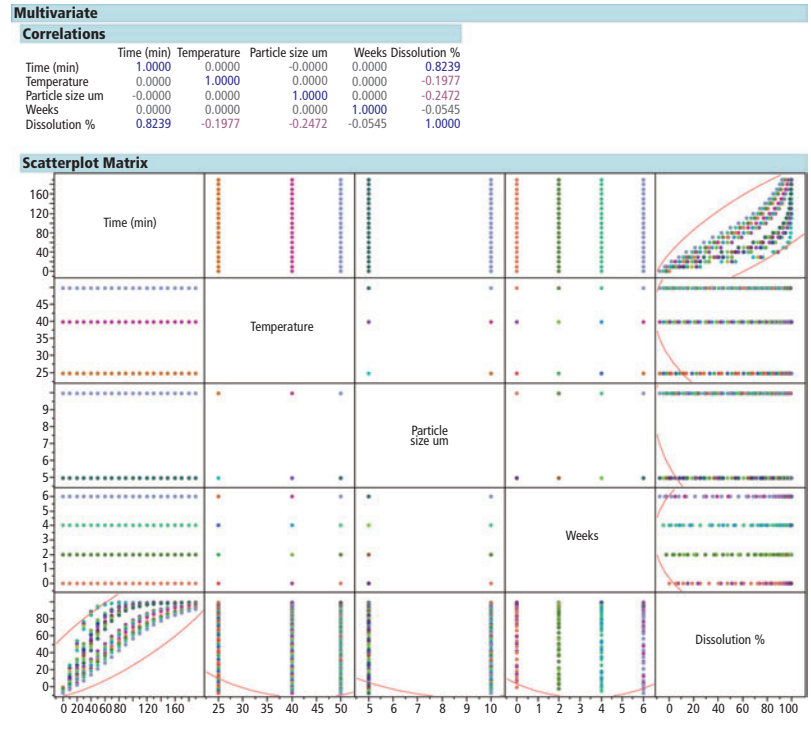
Proper design of experiments for data collection and curve isolation is crucial for building non-linear models. **Figure 1** illustrates the factors that should all be square relative to all other factors and have zero correlation relative to each other. For this tablet dissolution example, multiple time points (minutes), multiple storage conditions (temperature), multiple drug substance particle sizes, and multiple weeks were measured. Percent dissolution was the response of interest.

Analysis method

The following is a step-by-step procedure for non-linear stability modeling and expiry determination.

Step one. Measure the data at multiple time periods, using multiple particle sizes and at multiple temperatures. Generate a plot of the data to visualize the relationship of the curves over time (25-10-0: 25=Temperature, 10=Particle Size, and 0 = days) (see **Figure 2**).

Figure 1: Design of experiment structure and data structure visualization.



Step two. Fit each curve individually. In this example, each dissolution curve was fit using a four-parameter logistics (4PL) curve. The four parameters are: upper asymptote, lower asymptote, inflection point, and slope of the dissolution curve. R-Square should be high (typically above 0.95) and RMSE error should be low for each curve. Outliers should be checked using the residuals. Save the parameters of the curve. In this example, there are four parameters, upper asymptote, lower asymptote, growth rate (slope), and inflection point (see **Figure 3**).

Step three. Save the parameters from the curve and the factors that influence them into a table. For this example, the growth rate and inflection point are the coefficients that may change the most based on the factors under consideration. The upper and lower asymptotes are not of concern for this problem as all of the curves have similar lower asymptotes and similar upper asymptotes, but upper and lower asymptotes could be important for other problems, so generally it is best to model all of the curve parameters (see **Figure 4**).

Step four. Fit the curve parameters with a least-squares multivariate regression. Growth rate, the slope of the 4PL fit, and inflection point are the most important as the dissolution starting point and the upper asymptote are essentially the same for all curves. Main effects and interaction models generally work best and p-values and F tests can be used to evaluate each model term (see **Figure 5**).

Step five. Save the equation from the multivariate parameter model. An example of the inflection point model is in **Equation 1**.

Figure 2: Dissolution non-linear curve visualization.

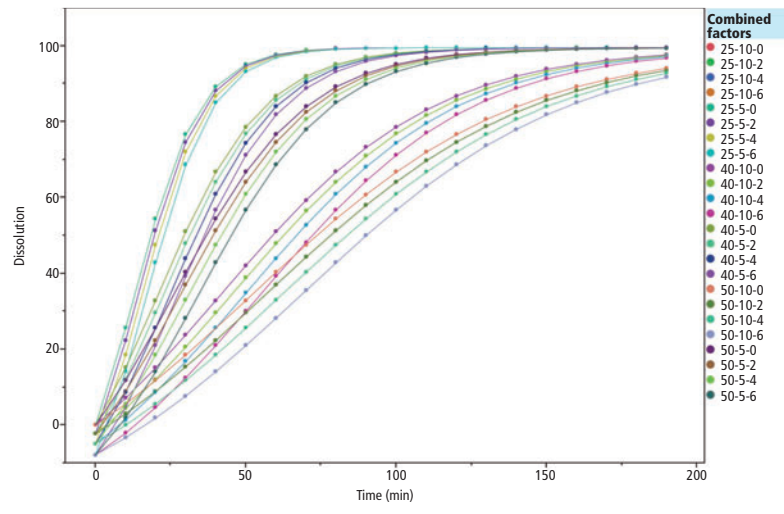
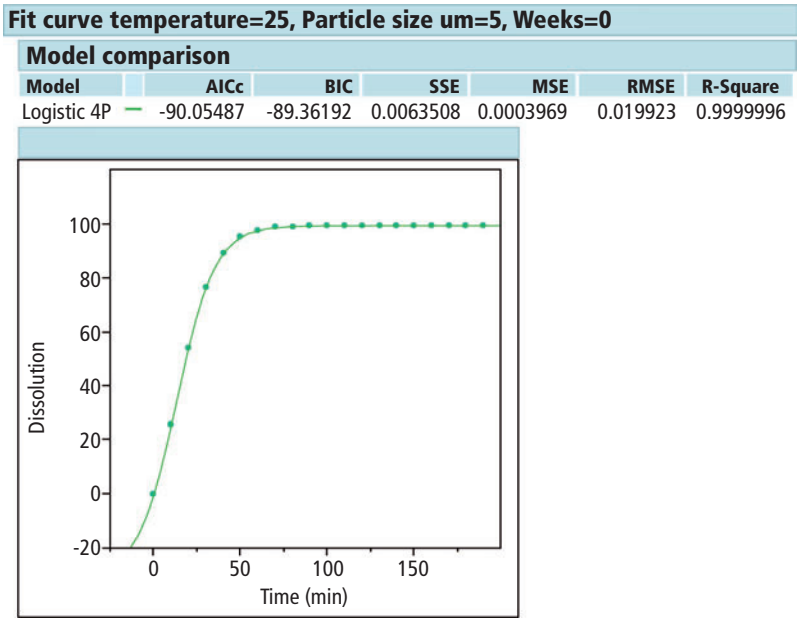


Figure 3: Individual non-linear curve.



Inflection point=

(-39.2209489504855) + 1.57872813205864 * :Weeks + 4.59873178679376 *:Particle Size um + 0.900151254288678 * :Temperature + (:Weeks - 3) *(:Particle Size um - 7.5) * 0.210156521957134 + (:Weeks - 3) * (:Temperature -38.3333333333333) * 0.0410230542148583 + (:Particle Size um - 7.5) *(:Temperature- 38.3333333333333) * 0.120412939953522

[Eq. 1]

Step six. Substitute the growth rate (slope) and inflection point coefficients from the multivariate model into the nonlinear prediction. The red box in **Figure 6** shows the substitution for the inflection point.

Step seven. Check the model to make sure it matches the actual data. Correct any modeling errors by add-

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Figure 4: Factor and parameter table.

Weeks	Particle size um	Temperature	Growth rate	Infection point
0	5	25	0.0909554588	13.065024341
2	5	25	0.0910094568	14.233400619
4	5	25	0.0910595834	15.597147637
6	5	25	0.0908862161	17.206979311
0	10	25	0.0454271318	26.087752474
2	10	25	0.0454824294	28.424488692
4	10	25	0.0455043466	31.130289669
6	10	25	0.0454248554	34.370306664
0	5	40	0.0568276703	20.912786212
2	5	40	0.056875087	22.756305618
4	5	40	0.0568915501	24.911843234
6	5	40	0.0567602727	27.479985058
0	10	40	0.028387009	41.775242277
2	10	40	0.0284056616	45.429904676
4	10	40	0.028426348	49.794527539
6	10	40	0.0283816079	54.935228092
0	5	50	0.0454271318	26.087752474
2	5	50	0.0454824294	28.424488692
4	5	50	0.0455043466	31.130289669
6	5	50	0.0454248554	34.370306664
0	10	50	0.022749618	52.286382315
2	10	50	0.022749952	56.816249935
4	10	50	0.0227666129	62.312506986
6	10	50	0.0227421152	68.737337419

Figure 6: Generalized non-linear dissolution model.

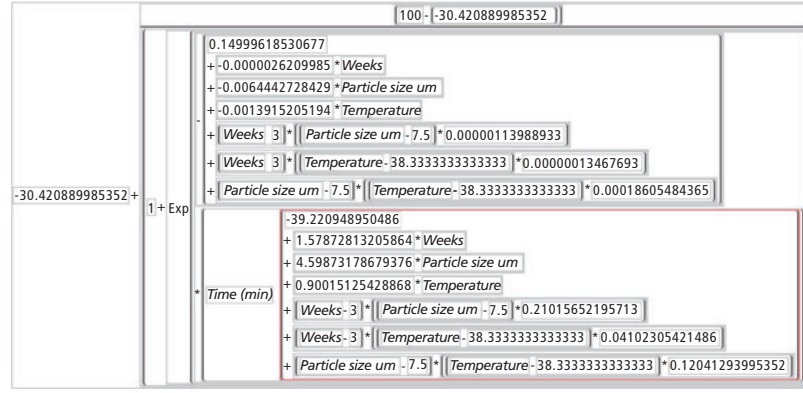


Figure 5: Parameter model quality.

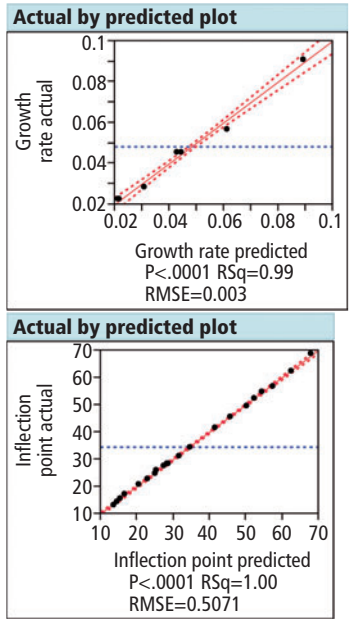
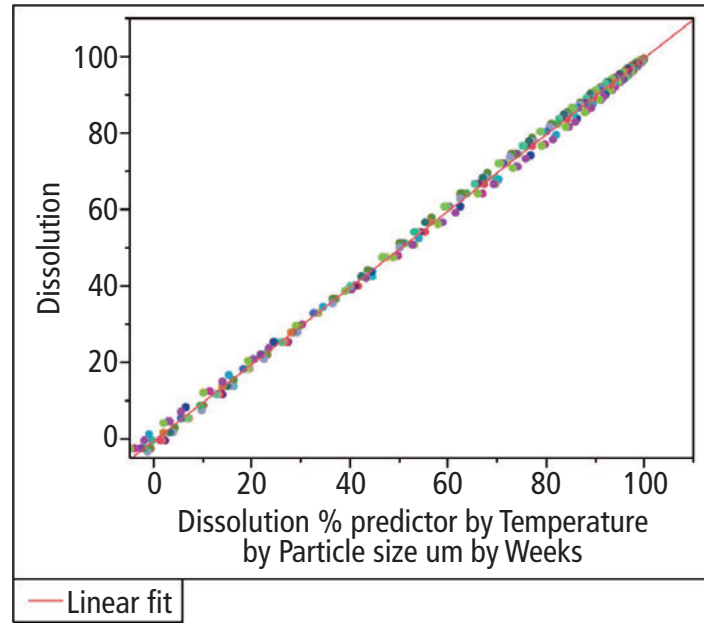


Figure 7: Model versus actual check.



ing or modifying a multivariate model term. A simple YX regression plot of the model versus the measurement will indicate model quality and any systematic errors (see **Figure 7**).

Step eight. Create a profiler from the equation to predict future dissolution rates. This can be done using a modern statistical package such as SAS/JMP (see **Figure 8**).

Step nine. Predict dissolution at any time, temperature, or particle size combination using the profiler. For this example, particle size was set to 5 μm, temp to 25 and time in weeks to zero. The dissolution time was fixed at 100 min with a specification of not less than 90% (see **Figure 9**).

Step ten. From the profiler at each time point (weeks), make sure the time (min) and particle size (5 um) are fixed, determine dissolution at the nominal temperature (non-accelerated condition). Fit the rate of degradation using either a linear or nonlinear model from the profiler predicted data. In this case, the rate of dissolution is not linear so a non-linear curve is fit to the data and the expiry is determined based on the extrapolated curve (see **Figure 10**).

The same method is used for predicting both the nominal expiry and the 95% CI expiry.

Step eleven. Finally, long-term stability evaluation at nominal storage conditions will be used to confirm the early model prediction and will provide an independent secondary determination of stability and changes in dissolution. Understanding rates of change should factor into shelf life and release specification limits (1).

Figure 8: Generalized multiple factor non-linear profiler.

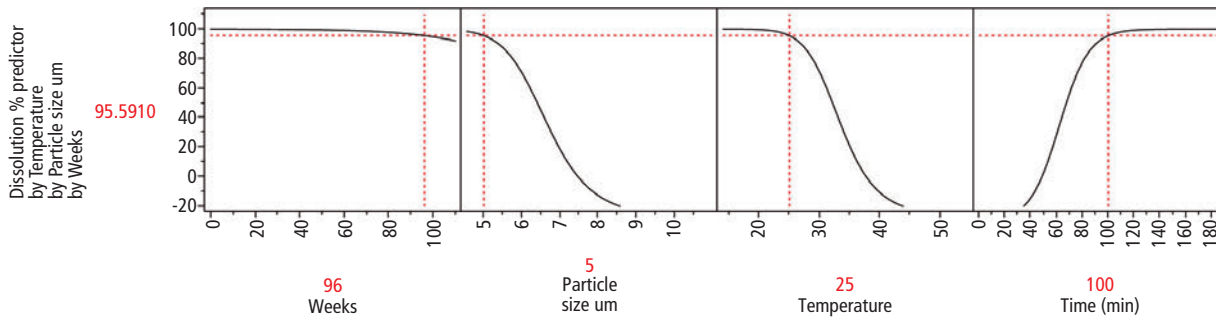
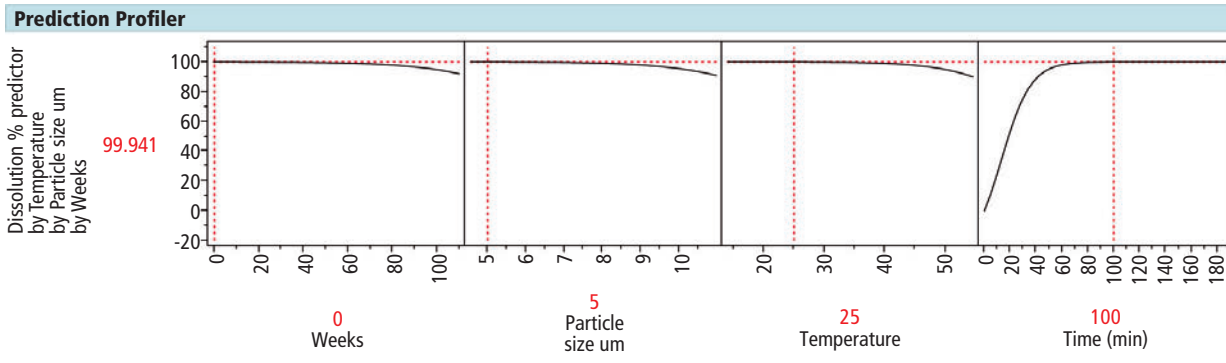


Figure 9: Disslution prediction from the model.



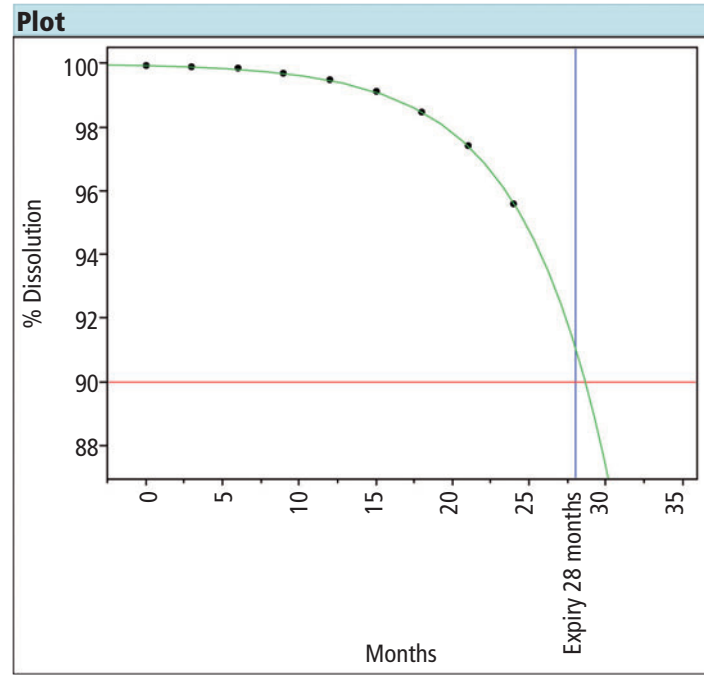
Summary

Non-linear multiple factor analysis has long been a problem in a variety of process and product modeling and prediction. The novel procedure discussed in this paper for the characterization of multiple factor non-linear product performance provides a clear, statistically defendable method for determining dissolution and accelerated stability. Long-term verification of accelerated conditions should always follow early determinations of expiry, acceleration rates, and rates of degradation.

Reference

1. ICH, *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (Oct. 6, 1999). **PT**

Figure 10: Expiry determination.



TECHNICAL Q&A: STERILIZATION

Sterilization of Blow-Fill-Seal Equipment for Aseptic Filling

Jennifer Markarian

Nitrogen dioxide can sterilize and depyrogenate an aseptic fill area in a blow-fill-seal process.

Blow-fill-seal (BFS) technology—in which a polymeric container is formed, filled, and sealed in one continuous process—has been used for more than 40 years to aseptically package parenteral pharmaceutical products, such as ophthalmic solutions. Use of BFS technology is expected to increase for packaging biologics, such as vaccines and protein-based materials. BFS is an automated system that minimizes human contact. Typically, the product-contact path of the BFS process is sterilized with steam, and the entire process takes place in a cleanroom environment. Noxilizer, which supplies nitrogen dioxide (NO_2) sterilization systems, and BFS equipment supplier Weiler Engineering recently presented research on NO_2 sterilization and depyrogenation of the fill area in Weiler's ASEP-TECH BFS systems using a Noxilizer NOX FLEX Rapid Biodecontamination System (1). *Pharmaceutical Technology* spoke with David Opie, PhD, senior vice-president of R&D at Noxilizer, and Chuck Reed, director of sales and marketing at Weiler Engineering, about this sterilization and depyrogenation method.

Sterilization and depyrogenation

PharmTech: What are some of the concerns for sterilizing BFS equipment?

Opie (Noxilizer): Aseptic processing requires rigorous and careful manufacturing practices due to the potential adverse effect on the healthcare consumer. Regulatory agencies are placing greater focus on improved patient safety and are developing standards to ensure sterile, contamination-free products. In particular, regulatory standards increasingly state that pharmaceutical manufacturers should be aware of new procedures designed to reduce risk to the product through the use of enhanced technology. One such procedure is the reduction of pyrogens during the decontamination process.

Pyrogenic contamination comes from endotoxins, which are mainly lipopolysaccharide components of Gram-negative bacterial cell walls that can cause acute febrile reactions. These endotoxins are heat stable and may be present even when viable organisms are no longer detectable. Endotoxins are impossible to eliminate from filled containers; thus, procedures are generally directed at eliminating endotoxins during the preparation process.

Reed (Weiler): The entire BFS process takes place in a cleanroom environment, and the product-contact path is sterilized in place with steam. The fill area of a BFS system is much different from the fill area of a conventional aseptic filling system, because the product is filled as soon as the container is formed, which reduces the opportunity for contamination. The critical filling zone area of a BFS machine is the area comprising the fill system shroud, which typically encompasses the fill needles and electronic modular dosing system. This enclosed area has typically been manually sanitized prior to the start of a production batch, and during production is supplied by HEPA-filtered air. We wanted to provide additional assurance for our customers of the decontamination of the fill area. The NO_2 process offers a new procedure for depyrogenation and decontamination of the fill area in a BFS system to give that additional assurance.

Advantages of NO_2

PharmTech: What are the advantages of using NO_2 to sterilize the BFS fill area?

Opie (Noxilizer): The room-temperature process combines decontamination of exposed critical zone surfaces with the potential for depyrogenation of these surfaces. The Noxilizer process is a fast (less than one hour), automated process that yields more than a six-log reduction in biological indicator organisms and more than a three-log endotoxin reduction (1). The NO_2 process is a true gaseous process that has more uniform distribution than vapor processes. Another feature of the NOX FLEX system verified in this study was the remote operation of the decontamination process with up to 50 meters of conduit between the NOX FLEX unit and the ASEP-TECH system, which permits the location of the Noxilizer equipment outside of the cleanroom in which the BFS machine is installed.

Reed (Weiler): BFS technology is well suited for aseptic processing of biologics, such as vaccines and protein-based materials, which are particularly sensitive to residual sterilant in the filling environment. NO_2 has been demonstrated to have a fast aeration rate that results in low residual sterilant. In addition, the automated NO_2 system eliminates the human interaction required in the manual sanitization method. Finally, the integrated system is an efficient process that can be more easily validated than the manual process.

Cycle parameters

PharmTech: What are the critical parameters of the sterilization cycle?

Reed (Weiler): The cycle parameters were developed to coincide with the normal cycle time of the clean-in-place/sterilize-in-place process for sterilizing of the product path in the BFS machine. The BFS cycle parameters for the study were 30 mg of concentrated NO_2, 55% relative humidity, a 40-minute decontamination time and 30-minute aeration time (1).

Reference

1. C. Reed, et al., "Decontamination and depyrogenation of an Asep-Tech Blow/Fill/Seal system," poster presented at the PDA Annual Meeting (San Antonio, TX, 2014). **PT**

STEVE GSCHMEISSNER/GETTY IMAGES

Delivering Biologics with a Difference

ON-DEMAND WEBCAST

Register free at www.pharmtech.com/difference

EVENT OVERVIEW:

As the biologics market continues to grow with additional launches, expanding indications, and approvals of biosimilars, the delivery platform will play a more critical role in product differentiation. In addition, today's clinical guidelines call for increased safety and simplicity in medication delivery. Market data demonstrates that delivery which provides convenience, from dose preparation to administration, can build clinician preference.

Due to complexity relating to heat-intolerance, biologics requiring intravenous dosing are typically reconstituted just prior to use. Aseptic-filling is a method which does not involve the use of heat for sterilization, and is a proven sterilization approach for commercial scale filling of biologics and other heat-sensitive molecules.

Baxter's proprietary GALAXY technology is currently the only manufacturer-prepared commercial scale aseptic filling process for premixed drugs in flexible IV bags, delivering the first-ever biologic in an intranvenous bag. This webinar will explore the advantages, challenges, case studies and science behind delivering biologics with a difference.

Who Should Attend:

- R&D/Formulation Developers
- Product Marketing / Brand Strategy Planners
- New Product Planners
- Mature Brand Planners

Key Learning Objectives:

- Learn about the possibility of delivering intravenous-dosed biologics in an aseptically-filled intravenous bag
- Increase your understanding of the business drivers and potential value added with this strategy
- Increase awareness for the timeline required and ideal lifecycle timing to implement

Presenters:

Sarah E. Lee, Ph.D.
Research Scientist
Pharmaceutical Development, Baxter

Sabrina Kader
Senior Marketing Manager
Baxter BioPharma Solutions

Moderator:

Rita Peters
Editorial Director
Pharmaceutical Technology

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For questions, contact Sara Barschdorf at sbarschdorf@advanstar.com

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Health Systems Raise the Bar on Reimbursing New Drugs

Jim Miller

As payers refuse to cover new drugs, CMOs take a hit.

The value of the customer relationship to a CMO is a function of two variables: unit volume and price per unit. Both variables are contentious issues: bio/pharmaceutical companies are putting enormous pressure on their CMOs for lower prices, while their inability to deliver forecasted volumes often means lost revenues for CMOs as reserved capacity goes unutilized. The resulting low margins depress CMO profitability and threaten their ability to raise capital and invest in replacement equipment and new facilities.

While low prices and missed forecasts often undermine the CMO-customer relationship, they reflect real challenges in the macro bio/pharma environment. Governments and private payers in North America and Europe are increasingly unwilling or unable to afford escalating expenditures on drugs. In Europe, governments have either pledged to reduce drug expenditures by national health plans or limit the growth of those expenditures to less than 5% annually. To ensure that budget targets are met, drug companies are forced to rebate some of the revenue realized from sales to national health programs when those purchases exceed targeted levels.

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In the US, there has been much press attention to the rapid rise in list prices for drugs, but the reality is that those list prices do not reflect what drug companies actually receive from their sales. A recent analysis by investment firm Credit Suisse found that major bio/pharma companies must give back 25–50% of the drug price in the form of discounts or rebates (1). Health insurance companies are getting tougher when negotiating pricing and are pushing more of the costs onto patients in the form of higher co-pays.

Decisions limiting or rejecting coverage for new drugs have hit CMOs hard.

A growing risk for bio/pharma companies is that a drug won't get covered at all. Payers are increasingly asking whether the incremental benefit of a new treatment is worth the high prices that bio/pharma companies are asking for new medications, especially cancer treatments. This development directly threatens the revenues and profits that bio/pharma companies expect their new product pipelines to be generating in the future.

Europe, especially the UK and Germany, is leading the way in restricting formulary access for new drugs. The leader in this process has been the UK's National Institute for Clinical Excellence (NICE). NICE evaluates drugs for inclusion on the approved formulary of the UK's National Health Service based on an analysis of clinical benefit relative to cost.

A recent PharmSource Trend Report found that NICE rejected 50% of the new oncology drugs it reviewed in the 2009–2013 period. Another third of oncology drugs were granted "Conditional Recommendation," meaning they would be reimbursed only for limited indications and/or with substantial discounts. Only 17% of oncology drugs reviewed during the 2009–2013 period were granted a full recommendation. Among non-oncology drugs, one-third received an outright recommendation for coverage but over half received a conditional recommendation (2).

While NICE does not set actual prices in the UK, its counterpart in Germany, the Institute for Quality and Efficiency in Health Care (IQWIG), does. Drugs that are deemed not to deliver additional clinical benefit are priced at the level of the comparator drugs already on the market, which are often generics. Bio/pharma companies have withdrawn some innovator drugs from the German market after receiving an evaluation of no additional benefit because they were unwilling to accept payment at generic-drug price levels.

Evaluations of new drugs by IQWIG have been similar to those by NICE. During the period 2011–2014 (first three months), IQWIG determined that 50% of the new drugs presented to it offered no additional benefit relative to drugs

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already on the market. A third were deemed to offer minor or non-quantifiable benefits, and only 10% were found to offer considerable benefit (2).

CMOs take a hit

Decisions limiting or rejecting coverage for new drugs have hit CMOs hard. PharmSource analysis found that nearly 60% of the rejected or limited drugs use a CMO for drug manufacture, and a similar percentage use a CMO for API manufacture. PharmSource estimates the lost CMO revenues amount to at least $250 million per year, and probably more: NICE and IQWIG evaluations are referenced by most other European countries, and even by Japan.

Drug companies and CMOs will take an even bigger hit as the US catches up with Europe in the evaluation of comparative effectiveness. The furor over the cost of Gilead's Hepatitis C treatment Sovaldi (contract manufactured by Patheon) has focused heightened attention on the cost/benefit trade-off. In recent months, the American Society of Clinical Oncology has begun its own initiative to evaluate the cost effectiveness of alternative cancer therapies as guidance for oncologists.

In the face of this increasingly difficult macro environment, how should CMOs respond? Their first response should be defensive by doing rigorous due diligence when determining pricing and contract terms for new drugs, especially new molecular entities. They need to understand whether the sponsor's expectations regarding price and volume are realistic given the high performance benchmarks erected by payers. They should be familiar with the coverage decisions that have been made regarding similar drugs, and they need to satisfy themselves that sponsors have reflected pharmaco-economic factors in clinical trial design and marketing plans.

Where coverage risks are high, CMOs may want to insist on take-or-pay or volume-based tiered pricing schemes to assure themselves a level of protection against adverse coverage decisions. They must also be relentless in their efforts to drive down their operating costs to protect their margins.

Price pressures and coverage limitations are immutable elements of the bio/pharma industry's macro environment. CMOs need to reflect those realities in their processes and operations if they are to succeed.

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1. S. King, "FirstWordLists: Which companies pay the highest US rebates and which companies are most dependent on US drug price increases?" www.firstwordpharma.com, May 11, 2014.
2. PharmSource, "Not So NICE: How Market Access Schemes in Europe are Impacting the CMO sector" (May 2014). **PT**

Using Engineered Particles in Capsules for Rapid-to-Clinic Dry Powder Inhalation Applications

ON-DEMAND WEBCAST

Register for free at www.pharmtech.com/drypowder

EVENT OVERVIEW:

Particle engineering via spray drying, combined with a formulation and process platform, allows for a bulk drug sparing approach to formulation and process development for drug delivery to the lung versus traditional crystalline lactose based delivery systems. Additionally different deposition targets—for example, the upper respiratory tract versus deep lung—can easily be achieved through particle engineering. In this webinar, experts will describe a pulmonary platform technology for the rapid development of inhaled formulations for early clinical trials. In addition, important aspects of the capsule interaction with the DPI device will be presented including the wide range of customization services to closely match customers specific requirements.

Spray-dried particle formulation development, spray dry process development, and encapsulation for early clinical studies will be explained. In addition, important aspects of the capsule interaction with the spray-dried powder will be presented. A case study using a model compound will be presented to demonstrate this platform approach.

Key Learning Objectives:

- Learn about formulations appropriate for engineered particles using the spray drying process.
- Review key aspects of developing and scaling the spray drying process.
- Understand critical features of specialty capsules appropriate for inhaled delivery of spray-dried powders.

Who Should Attend:

- Senior level executives working with dosage forms for pharmaceutical and biotechnology companies worldwide.

Presenter

Devon DuBose,
Technical Group Lead,
Bend Research

Dominique Cadé,
Director Polymer Science,
Research & Development Division,
Capsugel

Moderator

Jennifer Markarian,
Manufacturing Editor
Pharmaceutical Technology

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For questions, contact Sara Barschdorf at sbarschdorf@advanstar.com

Merck to Acquire Idenix

Merck and Idenix Pharmaceuticals, a biopharmaceutical company focused on the discovery and development of medicines for the treatment of human viral diseases, have entered into a definitive agreement under which Merck will acquire Idenix for $24.50 per share in cash. The transaction, which values the purchase of Idenix at approximately $3.85 billion, has been approved by the boards of directors of both companies.

Idenix's primary focus is on the development of next-generation oral antiviral therapeutics to treat hepatitis C virus (HCV) infection. The company currently has three HCV drug candidates in clinical development: two nucleotide prodrugs (IDX21437 and IDX21459) and a NS5A inhibitor (samatasvir). These new candidates are being evaluated for their potential inclusion in the development of all oral, pan-genotypic fixed-dose combination regimens.

Merck's research and development portfolio includes several HCV medicines in development, of which is a combination of MK-5172, an investigational HCV NS3/4A protease inhibitor and MK-8742, an investigational HCV NS5A replication complex inhibitor. The combination of these two investigational candidates has received breakthrough therapy designation from FDA for the treatment of HCV. In April 2014, Merck announced initiation of Phase 3 clinical trials for MK-5172/MK-8742 to evaluate the combination with and without ribavirin in various genotypes and across a range of patient populations with chronic HCV.

USP Helps Expand Worldwide Access to Tuberculosis Drugs

The US Pharmacopeial Convention (USP) and the US Agency for International Development (USAID) through the Promoting the Quality of Medicines (PQM) program have funded Capreomycin, the first "second line" anti-tuberculosis API for injectables. Capreomycin has been assessed by the World Health Organization (WHO) and given prequalification status.

Since 2009, USAID and USP, through the PQM program, have been providing technical and professional assistance to manufacturers and regulatory agencies in countries around the world to strengthen quality assurance systems for medicines, guide manufacturers toward compliance with WHO good manufacturing practices, and help manufacturers prepare product dossiers for submission to the WHO prequalification program.

As a result, the PQM program has helped three drugs achieve prequalification status including: Cycloserine, an anti-tuberculosis medicine; ZinCfant, a zinc product for managing diarrhea in children; and Capreomycin.

Grand River Aseptic Manufacturing Raises Funds for Expansion

Grand River Aseptic Manufacturing (GRAM), a CMO for aseptic pharmaceutical filling, received $9.8 million in capital to expand its facilities, which will create life-science jobs in West Michigan. Municipal Employees' Retirement System (MERS) of Michigan, a nonprofit organization, led the $9.8 million investment round, supported by other Michigan and Indiana-based investors.

"We are delighted with the strong investor response, especially by MERS," said Tom Ross, GRAM president in a press release. "Their considerable support, in combination with the backing from many private investors in our community, is a strong indicator that we're headed in the right direction. This funding enables us to expand our capabilities, improve our facility, and advance our customer reach, all while creating more highly technical, high-paying jobs in West Michigan."

Glenmark Pharmaceuticals Opens Monoclonal Antibody Manufacturing Facility

Glenmark Pharmaceuticals, a subsidiary of Glenmark Pharmaceuticals Limited based in India, has opened a new cGMP-compliant monoclonal antibody manufactuing facility in La Chaux-de-Fonds, Switzerland. This manufacturing facility supplements Glenmark's existing in-house discovery and development capabilities and will supply material for clinical development.

Glenmark Pharmaceuticals' Swiss research center has in-house capabilities and infrastructure for conducting antibody discovery, cell-line development, *in-vitro* testing and characterization of antibodies, process development, and analytical research. The new manufacturing facility supplements the R&D capabilities and will facilitate production of clinical grade material. The manufacturing facility has been designed for use of single-use bioreactor systems and also houses a suite for manufacturing cell banks.

Arecor and CPI Partner to Enhance Biologics' Compatibility with Containers

Arecor and the Center for Process Innovation (CPI) Biologics are working on a project to enhance the compatibility of biologics with their containers, and thereby, improve the stability and shelf-life of these medicines throughout transportation and storage.

The components of vials and syringes can adversely affect the stability of some biologics, causing degradation and making them unsuitable for administration. The collaboration between Arecor and CPI Biologics seeks to address this issue by determining the actual causative components and understanding the degradation mechanisms. The goal is to develop an efficient screening system that can detect compatibility issues during the development of new biologics. The tool kit will enable the determination of formulation and container selection strategies that will counteract these effects and ensure the stability of biologics in standard delivery devices.

The project starts with a proof-of-concept phase over a six-month period, and if successful, it could potentially transition into a development phase to establish standardized procedures and tools for the biopharmaceutical industry.

This is the first industry partnership that CPI Biologics has undertaken in association with the National Biologics Manufacturing Center (NBMC) and will be performed at CPI's Wilton laboratories and cleanrooms in advance of the opening of the NBMC in 2015.

3M Drug Delivery Systems

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Start-to-Finish Transdermal Development and Manufacturing Services

3M offers a continuum of services to meet the full spectrum of customer needs throughout the transdermal manufacturing process from robust process design to scale up and final product commercial manufacturing. Multiple 3M locations work together to provide a smooth transition from early development to commercial manufacturing:

1) Product development facilities that focus on the early stages of development
2) Process technology center—a pilot-scale facility focused on experimentation and process optimization
3) Commercial manufacturing site providing efficiency, quality and service.

All 3M facilities utilize scalable equipment and processes to minimize risk associated with site-to-site transfers.

Comprehensive transdermal product development and manufacturing capabilities allow 3M to be fully flexible to meet the requirements of customer projects. 3M works with customers at any stage of product development; whether it is a molecule for formulation in a transdermal system, a transdermal system ready for scale-up or an approved product for commercial manufacturing. In nearly any situation, 3M's experts are experienced in the processes necessary to transfer the technology and data, and perform the necessary regulatory work in a time-sensitive manner.

Emphasis on Quality

Lean Six Sigma methodology is a key factor in 3M's manufacturing efficiency. This discipline has been applied to manufacturing lines to achieve the most efficient layouts and material movements, and ongoing projects highlight ways to streamline operations, eliminate variation, and deliver a competitive advantage to customers.

3M Innovation Improving Every Life

As a trusted transdermal manufacturer, the global team of 3M Drug Delivery Systems experts is passionate about helping customers successfully bring cost-effective, high-quality, and patient-friendly products to market that will improve patients' lives.

3M Drug Delivery Systems has the experience, services, and capacity to meet your development and manufacturing needs. With our proven experience and commitment to quality and innovation, we stand ready to partner with you to develop your next successful commercial product.

Contact a 3M representative to learn more about how 3M's transdermal manufacturing and development process can help meet your transdermal product needs. Learn more at 3M.com/DDS.

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BioSpectra is a FDA-registered, cGMP-compliant, contract manufacturer and commercial producer of biological buffers, pharmaceutical excipients, and laboratory reagents.

BioSpectra manufactures pH stabilizing biological buffers for the biopharmaceutical industry, which have low UV absorptivity, minimal reactivity, stable pH, and high solubility in water.

The **excipients** offered by BioSpectra are produced in accordance with cGMP guidelines to provide the highest quality materials available to the biopharmaceutical industry. These excipients include tromethamine, tris hydrochloride, urea, ammonium sulfate, guanidine hydrochloride, MOPS, HEPES, MES, and other related intermediates.

BioSpectra's **laboratory reagents** undergo stringent product testing to ensure that customers receive only the highest quality material for use in their laboratory applications.

BioSpectra delivers the highest quality **custom manufactured products** using mutually established supply agreements and quality agreements including:

- Specifications—customer provided or BioSpectra developed
- Requested batch sizes from 1 Kg to 50,000 Kg and 100 mL to 20,000 L
- Versatile packaging options to meet customer needs
- Fast delivery of finished products

Our custom products are manufactured, packaged, tested, and approved in our secure, FDA-registered facilities to ensure contamination-free, traceable, reliable materials.

Synthesis

High Purity Crystalline Compounds

Our extensive line of manufacturing suites, qualified equipment, and advanced quality systems produce biopharm/pharmaceutical targeted versions of chemicals using ultra-purification methods, acid/base reactions, substitution chemistry, particle manipulation, and other synthesis.

Custom Solutions

Formulated based on customer requests and industry demand, BioSpectra's custom solutions are produced in closed, clean environments and can be sterile filtered into final packaging.

Purifications

Our process development team has more than 15 years of experience designing purification systems based on process parameters that achieve the correct, critical quality characteristics of the end product. Our extensive range of manufacturing equipment offers a safe home for your product from evaluation samples through bulk commercialization.

Particle Manipulation

Managing flow characteristics and dissolution rates requires consistent and defined starting crystals. BioSpectra uses the best available technology to manipulate crystals to meet your processing parameters. Current equipment includes our 316 S/S Fitz-Mill™, 316 S/S hammer mill, 316 S/S 30ft^3 rotary blender, 316 S/S air sieve, 316 S/S Jet Mill, and 316 S/S Ribbon Blender.

BIOSPECTRA

Brookfield Engineering Laboratories

www.brookfieldengineering.com

When powders fail to discharge reliably from bins and silos, plant managers lose sleep. These interruptions in production may lead to plant shutdown to correct the flow restrictions and stoppages. Unwanted variations in pack weight, mixture, and performance properties may necessitate rework of finished product.

What is the root cause of these flow problems? QC departments inspect incoming raw materials in powder form and measure particle size/shape and moisture content. Although the powders pass these tests, flow problems may still result. The issue is to perform a test that measures flow behavior.

Brookfield's Powder Flow Tester (PFT) is a single-solution instrument that solves this uncertainty. It uses a proven scientific method called the flow function test for analyzing flowability according to ASTM D6128. The instrument compresses and shears the powder, simulating what actually happens in the bin during flow. Data output categorizes the flow behavior as one of the following: free flowing, easy flowing, cohesive, very cohesive, or non-flowing.

Mathematical analysis of flow data by the PFT software calculates critical outlet dimensions for hoppers, namely outlet diameter and half angle. This determines whether existing plant equipment will work effectively or require modification to handle new powder formulations.

Bring peace of mind back to powder processing in your plant by using the Brookfield PFT to approve incoming materials and finished product.

BROOKFIELD

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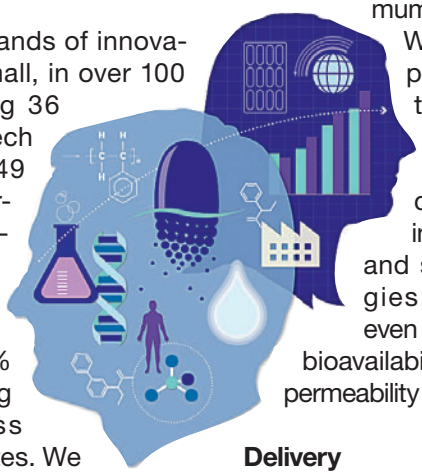
Catalyst + Talent. Our name combines these ideas. From drug and biologic development services to delivery technologies to supply solutions, we are the catalyst for your success. With over 75 years of experience, we have the deepest expertise, the broadest offerings and the most innovative technologies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

We serve thousands of innovators, large and small, in over 100 markets including 36 of the top 50 biotech companies and 49 of the top 50 pharmaceutical companies. Our team of over 1,000 talented scientists supports 40% of recent new drug approvals across nearly 30 global sites. We are the #1 global partner in drug development and a global leader in clinical supply solutions. Our significant intellectual property includes over 1,200 patents and patent applications.



Whether you are looking for a single, tailored solution or multiple answers throughout your product's lifecycle, we can improve the total value of your treatments—from discovery to market and beyond.

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

Development

With our broad range of expert services–including analytical, biologics, pre-formulation, and formulation–we drive faster, more efficient development timelines and produce better products. Our robust GPEx® mammalian cell line engineering technology accelerates large molecule drugs from discovery to clinic and our unique Optiform™ technology ensures maximum API optimization. With our deep expertise and our extensive formulation capabilities in oral dose forms, controlled release, inhaled dose forms and softgel technologies, we can solve even the most complex bioavailability, solubility, and permeability challenges.

Delivery

We are a world leader in drug delivery solutions with a proven track record of helping our customers create better treatments by boosting bioavailability, solubility, and permeability; improving ease and route of administration; and increasing patient compliance. Our unique delivery technologies–including softgel solutions, Liqui-Gels® capsules and Vegicaps® capsules, Zydis® and Lyopan® fast-dissolve, controlled release, including OSDrC® Optidose™ optimized dose delivery, and inhaled dose forms–improve how products work in and for patients.

Supply

As a seamless extension of your supply chain, we have the technology and expertise to offer global, integrated supply chain solutions. We manufacture oral, sterile, and inhaled dose forms, produce biologics for pre-clinical and clinical studies, and are a recognized leader in

clinical product packaging. We help ensure the highest quality of product as well as speed your time to market. With our expertise and capacity across every phase of development, we offer you the peace of mind that comes from having one company manage your supply chain throughout your product's entire lifecycle.

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www.caronproducts.com

Caron Products & Services, Inc. has provided high-quality temperature control solutions to a variety of markets since 1985. Caron's standard product line includes: Environmental/Stability Chambers, Photostability Chambers, Refrigerated Incubators, Diurnal Incubators, CO_2 Incubators, Plant Growth Chambers, and other environmentally controlled chambers/incubators.

Caron developed exclusive earth-friendly technologies that contribute to unmatched efficiency, energy, and cost savings.

gROD™

- gROD is Caron's Refrigeration on Demand controlled refrigeration, and it efficiently manages power consumption and saves electricity.
- Unlike competitive units that run refrigeration constantly to maintain required setpoints, gROD only operates the refrigeration system when it is needed to maintain the temperature setpoint.

gVapor™

- gVapor injects humidity only as needed, without utilizing steam to create humidity, using much less energy than other technologies.
- Unlike competitive units that incorporate energy inefficient steam generators to control and create humidity, gVapor atomizes water into humidity vapor in small, controlled amounts.
- gVapor quickly recovers humidity after door openings.

Other earth friendly, cost-saving design features

- Our 115V units run on standard laboratory electrical outlets, reducing the amount of energy required to run the chamber.
- The Environmental Chambers are insulated with energy efficient high R, CFC-free foam, contributing to high thermal retention, and tightly controlling the conditions inside the chamber. Heat loss is significantly eliminated, which places less demand on your laboratory's air conditioning unit.
- All units have a heated, triple pane, argon filled glass door, which meets the new Department of Energy standard for refrigerated equipment. The energy efficient door heater also minimizes condensation on the door for a clear view of your product and aids in temperature recovery.

To download our new white paper, "Getting a Handle on 'Green' Purchases for Your Lab: How to Select an Environmentally Preferable Chamber and Incubator," based on the presentation given at the 2012 NIH Sustainability Conference, visit www.caronproducts.com/white_papers.

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For pharmaceutical companies seeking solutions to achieve clinical and commercial success, DPT and Confab offer an unmatched breadth of service and vast experience in resolving development and manufacturing challenges in sterile, non-sterile, semi-solid, liquid, and complex solid dosage forms. Through our specialized Centers of Excellence, we're tenacious about discovering solutions and maximizing efficiencies. By asking the right questions and thoroughly investigating your options, our experts give you the answers you need from development through commercialization.

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NON-STERILE		
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EXTRUSIONS	●	○
TABLETS	○	●
CAPSULES	○	●
LIQUID FFS	○	●
SUPPOSITORIES	○	●
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CREAMS	●	●
EMULSIONS	●	●
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Fette Compacting America

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Fette Compacting America Introduces the FE75 Tablet Press, Offering Peak Performance for Large Batch Production

Fette Compacting America, the leading supplier of tablet press equipment for pharmaceutical and nutritional applications, has introduced the FE75 Tablet Press, a double-sided rotary press that can be equipped with up to 115 punch stations to produce more than 1.6 million tablets per hour. Ideal for the premium production of large batches, the FE75's four compression rollers feature a special control system for direct compression, enabling the machine to operate with two intermediate pressures.

The FE75 Tablet Press shares several technologies with the FE Series' other two machines, the FE35 and FE55. Common features include a new, patent-pending conical filling unit, highly accurate manually adjustable filling table, innovative compression rollers, trouble-free tablet discharge through the column, a revamped operating terminal, and the connection of process equipment through a standardized plug-and-play interface.

With a footprint of only two square meters, the FE75 also sets new standards in terms of its size and space requirements.

Minimum Product Loss & Contamination Protection

The FE75 Tablet Press features a variety of upgrades unavailable through class competitors. For example, new pneumatically controlled tablet scrapers guarantee a constant surface pressure and minimize product loss. New conical filling units allow for easier, safer processing of complex product mixtures, and tablet contamination is significantly hindered by a groundbreaking lubrication system that separates the lubrication of punch head and punch shaft in combination with a closed cam track system.

TRI.EASY Design for Simple Operation

Like the FE Series' other presses, the FE75 embodies Fette Compacting's TRI.EASY design concept, which focuses on the user and ensures trouble-free production irrespective of an operator's experience and qualifications. For example, all steps involved in turret changeover have been automated or designed for tool-less execution. All machine supply lines are connected by multifunctional plugs, and its design delivers excellent accessibility to all components.

FETTE COMPACTING

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The GEMU 4242 is a combination two-way pneumatic valve switchbox and position indicator. This latest generation microcontroller-based switchbox and position indicator is ideally suited for smaller and medium-sized applications.

- LED position indicators allow the housing to glow green for open and orange for closed. The high visibility LEDs makes it easy for the operator to see the position of the valve from several feet away.
- Location function enables the 4242 to continuously flash green to allow easy location of the switch.
- The 4242 has a valve stroke length of 2-30 mm.
- Various fault conditions have been coded with LEDs making it easy for the operator to troubleshoot any issues that may arise.
- End position and stroke speed programming can be accomplished remotely or at the switch using a magnet.

While Gemü is committed to the pursuit of quality and excellence in the development, production, and manufacturing of engineered diaphragm valves, we strive to consistently provide a level of service exceeding the expectations of our customers. Every inquiry and order is carefully considered so the customer can be offered the most suitable Gemü products to match their requirements. Gemü's overriding philosophy is to ensure each and every customer contact is a quality experience.

Agency approvals:
ISA 12.12.01 Nonincendive Electrical Equipment for Use in Class I and II, Division 2 and Class III, Divisions 1 and 2 Hazardous (Classified) Locations
CSA C22.2#213 Nonincendive Electrical Equipment for Use in Class I, Division 2 Hazardous Locations
UL 61010-1 Safety requirements for electrical equipment for measurement, control and laboratory use
CSA C22.2#61010-1 Safety requirements for electrical equipment for measurement, control and laboratory use

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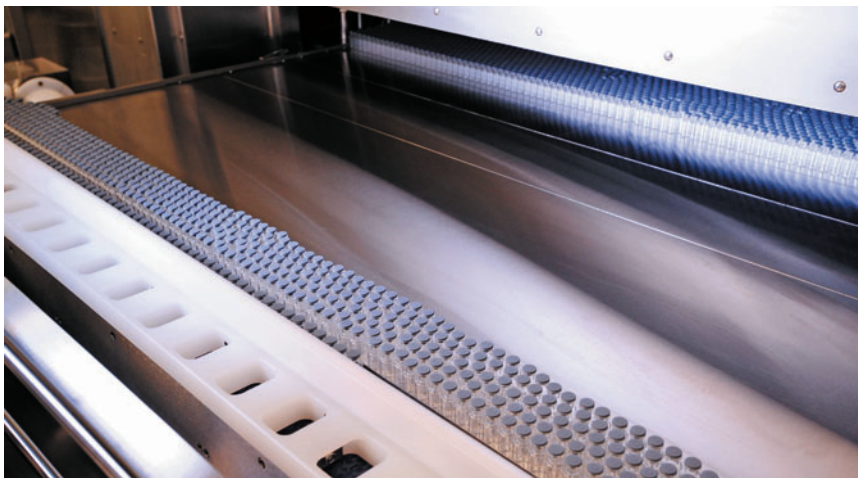

Jubilant HollisterStier is a global manufacturing service provider, able to aseptically fill liquid, lyophilized, semi-solid, and solid dosage forms in our facilities across North America and India. Jubilant HollisterStier represents the CMOs formally branded as HollisterStier Contract Manufacturing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

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

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

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

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

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

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

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

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

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Julabo USA

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Superior Temperature Control for a Better Life

JULABO is a manufacturer of liquid temperature control instrumentation producing temperatures from –90˚ to +350˚C, providing quality devices for research, science, and process in many industries such as, but not limited to pharmaceutical, specialty chemicals, petro-chemicals, medical devices, and semiconductors. **JULABO products include heating and refrigeration circulators, chillers, high-temperature circulators, and water baths.** Julabo USA is ISO 9001 certified. This will ensure that the customer gets a quality product for every purchase. The use of JULABO temperature control instruments increases reliability, accuracy, and reproducibility.

Highly Dynamic Temperature Control Systems by JULABO

The new PRESTO® systems are designed for precise temperature control as well as rapid temperature changes, making them ideal for reactor vessels, material stress tests, or temperature simulations. These instruments cover a working temperature of -92 to +250°C with high cooling and heating capacity. Highly efficient components give these instruments the ability to compensate for exothermic and endothermic reactions with extraordinary speed. Permanent internal monitoring and self-lubricating pumps contribute to the new PRESTO®'s long service life.

The integrated 5.7-inch color industrial-grade touch panel is one of the identifying characteristics of the new PRESTO®. It gives the user a clear and well-organized view of important information while greatly improving user-friendliness. Once in operation, the new PRESTO® units are whisper quiet and barely audible in a laboratory. The new PRESTO® units are extremely robust and work reliably even if the ambient temperature climbs as high as +40 °C.

JULABO is committed to design superior temperature control for a better life.

Julabo
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Meissner Filtration Products

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Meissner is your source for innovative microfiltration and single-use systems. We are focused on advancing technology, and by leveraging our R&D efforts, we are able to offer products that deliver advanced processing and fluid handling solutions to the pharmaceutical and biopharmaceutical industries.

Demonstrating our commitment to manufacture products for today's biopharmaceutical manufacturing operations, our TepoFlex® PE based biocontainers are designed to deliver the highest levels of fluid integrity provided by any existing product in industry. By engineering slip agents out of the TepoFlex® film and biocontainer manufacturing process, we substantially reduced the film's overall extractables profile, while also imparting remarkable visual clarity to the biocontainer. Providing the industry's highest combined gas and water vapor barrier, TepoFlex® biocontainers mitigate the risk of product degradation due to gas exchange, and concentration loss due to water vapor egress. TepoFlex® biocontainers are designed to be durable and impact resistant with over 95% of the film's strength retained in the seams where there is the greatest potential for a breach of fluid integrity.

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

Meissner's UltraSnap® filter assembly drives innovation by making the scale of single-use filters virtually unlimited. The assembly securely bundles multiple pre and final filters into a presterilized filtration system for plug and play use. UltraSnap® maximizes scale-up and processing possibilities by delivering the ability to configure filter capsules from 10 inches to 50 inches in length. For more information visit www.meissner.com.

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Who We Are
Micron Technologies offers contract particle size reduction and analytical services exclusively for the pharmaceutical industry. Particle size reduction by micronization or mechanical milling continues to be the preferred choice for increasing the dissolution rate of poorly soluble drugs, improving the content uniformity of oral solid and liquid dosage forms, and enhancing the performance of inhalation pharmaceutical products. Micron Technologies is committed to being the industry's Provider of Choice by offering the highest level of service and technical expertise along with the finest facilities.

Micronization/Milling Services
Micron has the capability to process gram to ton quantities of APIs with high product yields. Processing takes place in segregated independent processing suites which are climate-controlled. Available equipment includes jet mills, loop mills, pin mills, hammer mills, co-mills, and opposed jet classifier mills. This equipment can also be used inside custom designed containment areas to allow for the processing of highly potent compounds (OEL under 1 microgram).

Contract Laboratory Services
Micron's analytical laboratory provides extensive material characterization testing including particle size analysis by laser-diffraction, DSC, DVS, TGA, BET surface area analysis, X-ray powder diffraction, and scanning electron microscopy (SEM). Additional services include method development, method validation, release testing, and stability testing along with expertise in traditional techniques such as HPLC, GC, dissolution, etc. Micron's analytical services are also offered independent of milling services.

Facilities
With two modern, directly compatible facilities in the United States and United Kingdom, Micron Technologies provides a truly global capability. Both facilities have been inspected by the FDA, EMEA, or MHRA and PMDA Japan. To learn more about Micron's global capacity for micronization and milling services and state-of-the-art material characterization laboratories, please visit www.microntech.com.

Micron Technologies, Inc.
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Malvern, PA 19355
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PDA Education—Where Excellence Begins

www.pda.org/courses

The Parenteral Drug Association (PDA) provides worldwide education, training, and research opportunities in pharmaceutical, biopharmaceutical sciences, and their associated technologies.

Relevant Courses

PDA's curriculum includes more than 60 classroom and laboratory courses designed to meet the challenges faced in the areas of aseptic processing, biotechnology, environmental monitoring, filtration, validation, quality assurance, and regulatory affairs. Many of the courses occur in conjunction with PDA's annual workshops and conferences in the US and around the globe. Others are offered in the Training and Research Institute in Bethesda, Maryland. Additionally, PDA can tailor courses to a specific corporation and present them in-house.

Learn from Industry Experts

The lecture and laboratory courses offered by PDA give students the opportunity to learn from researchers, scientists, and industry leaders who developed the process, created the methods, or wrote the book on which the course is based. In fact, many of the labs and lectures are developed from the growing number of scientific technical reports produced by volunteer experts working with PDA's science and regulatory team.

Lab Offers Practical Applications for Learning

PDA created the Training and Research Institute to fill the need for hands-on, intensive, and job-focused training. Inside the Training and Research Institute laboratories, students practice what they've heard and seen in the classroom. PDA's laboratories include a fully functional aseptic processing suite that closely simulates a real-world manufacturing facility.

In the microbiology lab, students use the Vitek2 Compact, Laminar Flow Hoods, Biosafety Cabinet, incubators, and microscopes to perform tests typically carried out in a Quality Control Microbiology lab.

The biotechnology lab, where students learn courses such as virus filtration, formulation, and fermentation technology includes equipment such as small-scale bioreactors/fermenters, visual inspection booths, and a purified water system.

The CIP Lab includes a CIP Skid and syringe filling equipment. Here, students gain hands-on experience in validation of biotech-related cleaning processes and prefilled syringe technology.

PDA®
Parenteral Drug Association
Connecting People, Science and Regulation®

ADVERTORIAL

Patheon Inc.

www.Patheon.com

Patheon is a leading provider of contract development and commercial manufacturing (CDMO) services to the global pharmaceutical industry for a full array of solid and sterile dosage forms. Patheon, a DPx Holdings B.V. business unit, encompasses the combined CMO capabilities and pharmaceutical product development services (PDS), as well as the Biosolutions and Biologics (BIO) business.

Biologic Drug Substance Capabilities

From pre-clinical development to commercial supply, Patheon is an industry leader in the development and manufacture of mammalian cell-culture drug substances. Patheon offers biotech and pharmaceutical companies the ability to pursue opportunities around the globe with a fully integrated network of facilities. These world-class cGMP sites feature USP and DSP processes and technologies that enable us to meet your preclinical, clinical, and commercial milestones and goals for even your most challenging projects. With unmatched flexibility, Patheon gives you access to a breadth of options and technical expertise in biologic drug substance that will transform your expectations for yields, time to market and costs, that is supported by sterile manufacturing, including aseptic filling and lyophilization:

- Process and analytical development of mammalian cell-culture drug substances
- Clinical and commercial cGMP manufacturing via fed-batch, perfusion and XD®
- cGMP and non-cGMP supply.

Pharmaceutical Development Services

Patheon enables its customers to bring drug candidates from preclinical stages through to clinical trials, the NDA approval process and, if approved, commercial manufacturing. Patheon offers the full breadth of advanced scientific and preformulation services through to late development in solid and sterile dosage forms, as well as specialized capabilities in high potency, controlled/sustained release, and sterile manufacturing, including aseptic filling and lyophilization. Very few CDMOs can bring this big-picture perspective to building success into both solid and sterile pharmaceutical products. We give you access to a remarkably wide selection of formulation technologies:

- Conventional and specialized oral solid dose formats, including softgels and softgel technologies
- Liquid and lyophilized sterile products, including prefilled syringes and cartridges
- High potency products and controlled substances
- Solubility and bioavailability enhancement expertise.

Commercial Manufacturing Capabilities

As the global leader in large-scale pharmaceutical manufacturing, Patheon offers extensive commercial capabilities and capacity for drug product manufacturing. We have a global network of 12 fully integrated world-class commercial scale facilities—all preapproved by international regulatory agencies, and all maintaining the highest standards of quality and service. We take pride in our steadfast reliability and unmatched regulatory track record, but also in our spirit of innovation, as demonstrated by our introduction of the world's first sterile backup supply service. Over the course of nearly 40 years, Patheon has earned the trust of the most quality-conscious pharmaceutical companies by being able to provide exceptional service in:

- Large-scale capabilities and capacity at facilities around the world
- Wide variety of solid, sterile, and softgel dose forms
- Award-winning technology transfers and scale-up
- Expertise in complex formulations, controlled substances, and highly potent compounds
- Primary and secondary packaging.

Patheon

Performance the World Over

Ross, Charles & Son Company

www.mixers.com

Corporate Description
Ross's investment in its people and facilities for over 170 years has yielded a proud history of innovation in sanitary mixing, dispersing, emulsification, and drying. In the early 1900s, Ross introduced the "Pony Mixer," the world's first change-can mixer. With the "Versa-Mix," Ross was the first to offer the flexibility and efficiency of three independently driven agitators in one piece of mixing equipment. The "Mega-Shear" ultrahigh shear rotor-stator mixer and the "SLIM" high-speed powder injection system have advanced processing productivity even further. Today, Ross innovations also are producing significant advances in discharge systems, storage tanks, pressure vessels and reactors, and integrated process control systems.

Technical Services
The Ross Test and Development Center is fully equipped to simulate virtually any mixing application. Experienced engineers in the Ross Technical Services Group work with clients to find the right equipment configuration for their applications. A trial or rental will enable you to confirm mixing strategies in clients' plants and on their process lines.

Facilities
Ross is well-equipped to solve virtually any sanitary mixing, blending, or drying problem quickly. In the United States alone, Ross operates five plants, one of the best-equipped test centers in the mixing equipment industry, and a vigorous R&D program. Each of Ross's plants is fully equipped with CAD engineering support, fabrication capability, and advanced CNC machine tools.

Major Products
The Ross product line includes a broad range of mixer and blender designs as well as storage tanks and reaction vessels. Ross mixing and blending products for pharmaceutical applications include:

- **Turboemulsifier**: Combining a counter-rotating coaxial agitation system and a centrally mounted high-shear emulsifier in a mix vessel with a hemispherical bottom, it is suited for many applications, from the gentle blending of shear-sensitive materials to emulsification. Capacities of 10–4000 L are available.
- **Ross vacuum mixer homogenizer:** A fully integrated plant for producing creams, lotions, gels, and semisolids for the pharmaceutical, cosmetic, and personal care industries.
- A full line of **Tumble Blenders**.

Markets Served
Ross products are built on five continents. The company is proud to say that Ross products are helping to build greater productivity in virtually every major processing market around the world.

ADVERTORIAL

Sartorius Stedim Biotech

www.sartorius.us

Growing adoption of single-use bags for the production of biopharmaceutical drugs raises new challenges like consistent product quality, improved assurance of supply, robust change management, and business continuity planning. In close collaboration with resin and film suppliers, Sartorius Stedim Biotech's polymer scientists and biologists have followed a quality-by-design (QbD) program for the development of a completely new polyethylene film (S80), thus achieving consistent performance of the new Flexsafe bags for all bioprocess steps and applications. The partnerships and agreements with our suppliers, the complete understanding and control of our manufacturing process from the resin and the film extrusion to the final sterile bioprocessing bag, are the pre-requisites to ensure reliability of our supply chain. This assurance of supply relies on a long-term contract with our film supplier. In addition, the establishment of resin specifications instead of general trademarks provides robust change control and facilitates change management as we can rapidly validate an equivalent resin in the case of a discontinuation of a raw material.

A partnership, material science, and quality-by-design approach

In order to meet current industry challenges for single-use and a more robust product quality, a new proprietary PE S80 film and Flexsafe bag family have been developed in partnership with Südpack, our film manufacturer. With Südpack, we have established direct contacts and trust with selected industry leading suppliers of resins, providing us with an unprecedented level of information on the resin, and additive package formulation as a key part of our new strategy to achieve complete control of our entire supply chain, from the raw materials to the finished products.

Complexity of the supply chain

The assurance of supply for our Flexsafe bags is guaranteed by our long-term supply contracts established with our different resin suppliers and with Südpack. We have a 10-year supply agreement in place for the S80 PE film and a last-time buy option for a minimum of two years of resin demand in case of a change or discontinuation. With Südpack, we also benefit from the large state-of-the-art film extrusion capacity that is required to sustain the double-digit growth of the demand for single-use bioprocessing bags every year. Here again the complete control of our supply chain and of our manufacturing processes, from the raw materials to the final assembly, is critical to offer both quality and assurance of supply.

Global approach to quality, assurance of supply, change control, and business continuity

Sartorius Stedim Biotech has been working over the past few years to enhance quality, assurance of supply and change control for our single-use bags and intelligent single-use solutions including bags, filters, tubes, connectors, sensors, process analytical tools, and hardware.

Our Flexsafe bag range is a new benchmark, meeting the most stringent customer needs for safe bioprocessing.

sartorius stedim biotech

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Savillex

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High Performance Fluoropolymer Bottles for Single-Use BDS Storage Applications

Fluoropolymer (PFA and FEP) bottles are now widely used in the pharmaceutical industry process stream for the storage and transfer of pharmaceutical intermediates including API. Fluoropolymers are ideally suited to these applications due to their chemical inertness, wide working temperature range (-200°C to 260°C), and cleanliness. The new Purillex™ range of PFA and FEP bottles from Savillex Corporation have been designed specifically for biopharma use and feature several unique benefits not found in any other fluoropolymer bottle. Purillex bottles are manufactured by a unique stretch blow molding process that provides several key benefits compared with traditional fluoropolymer bottles manufactured by extrusion blow molding. Stretch blow molding is a two-step process that enables much more precise formation of the bottle neck and thread. In combination with a greater thread engagement (more thread turns), this gives Purillex bottles a much higher integrity seal, which is maintained over longer periods and across a wider temperature range, and eliminates the need for cap liners. Purillex bottles are manufactured using only virgin fluoropolymer resin and feature a pharmaceutical industry standard GL45 closure. Manufactured and bagged in an ISO Class 7 cleanroom, Purillex bottles also offer unmatched freedom from particles and particulate inclusions.

Purillex bottles are available in sizes from 50 mL up to 2 L, in both PFA and FEP. Closures can be modified to accept inserts to enable aseptic filling.

Savillex also produces a range of PFA vials from 1 mL upwards for stability studies and lot retention samples.

Purillex bottles are non-cytotoxic and USP Class VI compliant, and ship with full lot manufacturing certification. To support end-user validation for product-contact applications, they have been subjected to extensive organic and inorganic extractables testing by a thirdparty laboratory. Extraction tests using multiple solvents at elevated temperatures over 28 days were carried out. A summary of the test results, along with the methodology used, is available from Savillex.

Savillex
Purillex

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STERIS

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Got Rouge? STERIS Can Help
Our formulated detergents, application experience, and technical support can help your company:

- Optimize your cleaning and stainless steel maintenance program
- Maximize production uptime
- Enhance and maintain the condition of your stainless steel process equipment
- Minimize the introduction of non-validated products and processes.

A DIFFICULT INDUSTRY CHALLENGE

Pharmaceutical manufacturing facilities house some of the world's most advanced stainless-steel equipment. Stainless-steel corrosion, or rouge, is an industry-wide problem that, left untreated, can cause:

- Problems with equipment cleaning and validation
- Equipment downtime
- Reduced equipment life
- Product contamination.

Removing rouge and enhancing the corrosion resistance of stainless-steel equipment are essential preventative maintenance requirements for any manufacturing facility.

DEROUGING AND PASSIVATION CONSIDERATIONS

Developing a successful procedure for derouging and passivation requires a careful balance of many factors including:

- The ability to successfully remove any visible rouge
- Process constraints (e.g., temperatures and flow rates)
- Avoiding damage to surface finish caused by excessively aggressive chemistries
- Operator safety when handling hazardous chemicals
- Environmental concerns (e.g., phosphates and volatile compounds)
- Adherence to industry standards (e.g., ASTM A 967)
- Concerns related to the use of chemicals that are not part of the validated process cleaning operations.

STERIS OFFERS SOLUTIONS

Derouging

Removing rouge from process equipment can be very easy in some cases and extremely difficult in others. Therefore, there is no single "recipe" for performing a successful derouging operation. STERIS has developed a model operating procedure that consists of the following steps:

- A laboratory-based assessment to establish effective derouging parameters
- A robust alkaline cleaning to remove organic residues
- An acid treatment to remove iron oxides
- Process monitoring to assess the effectiveness of the treatment.

Passivation

Although passivation will occur spontaneously in the presence of oxygen, it can be enhanced with the use of chemical treatments. Analytical techniques like x-ray photoelectron spectroscopy (XPS) are commonly used to quantify the depth and quality of this passive layer by measuring the chromium-to-iron ratio (Cr/Fe). Using our recommended derouging procedure, STERIS has shown that both CIP 200® and ProKlenz® TWO Acid detergents are effective for stainless steel passivation.

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Science & Solutions for Life

Veltek Associates, Inc.

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Veltek Associates, Inc, (VAI) address the needs of pharmaceutical and biotechnology industries with viable monitoring equipment that effectively determines environmental quality levels to ensure facilities meet required standards.

SMA ATRIUMS are the core component to VAI's viable monitoring equipment. They are sterilizable 316 L stainless steel capture devices that are connected to controlled vacuum sources, such as the **SMA OneTouch® ICS.** Air is directed from the environment to impact onto a media plate contained inside of the SMA Atrium. The media plate is then evaluated to determine the number of viable organisms per cubic foot or liter of air.

Veltek is proud to introduce the **SMA OneTouch Integrated Control System (ICS).** This computerized, viable air monitoring system features a state-of-the-art touchscreen interface that provides full-featured, accurate, automated controls, or all aspects of the sampling process.

SMA MicroPortable™ air samplers are battery powered, compact, and lightweight which allows them to be easily moved to desired air sampling points. They combine the extended sampling capability of the SMA Atrium with calibrated air flow and digital readout that is factory programmed in CFM or LPM.

SMA® compressed air/gas samplers are portable, battery powered, microbial air samplers that collect samples from compressed air and gas sources. They monitor and regulate air flow and can sample from compressed air/gas lines up to 100 psi.

SMA ATRIUM

SMA Digital Display Control Centers (DDC) control calibrated and timed vacuum sequences to SMA Atriums. SMA DDCs provide strict regulation of air flow (1 CFM) and will visually and audibly alarm the operator if the proper air flow is not maintained.

SMA OneTouch Control Panels and **SMA In-Line Flow Switches** are wall-mounted controls used to remotely interface with SMA DDCs.

SMA ONETOUCH ICS

VELTEK ASSOCIATES, INC.

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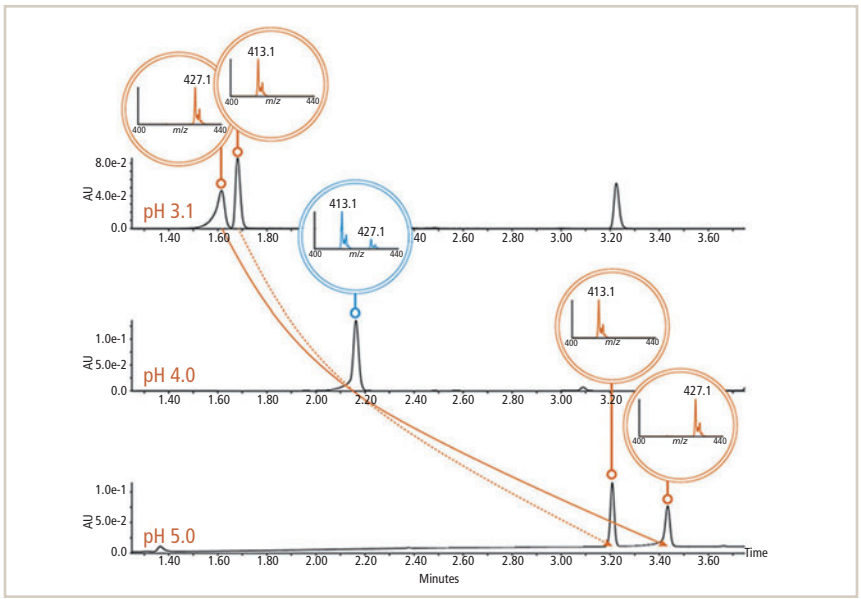
ACQUITY QDa Detector

ACQUITY® QDa™ Detector is as intuitive as an optical detector, with the robustness to handle all of your analyses. Working in harmony with your chromatography, it is pre-optimized to work with your samples, without the sample-specific or user adjustments typical of traditional mass spectrometers. For the first time, any analytical scientist can consistently generate the highest quality mass spectral data, routinely without the need for any special training or expertise, thus eliminating any need to contract out and wait for results from specialist analytical service laboratories.



With the ACQUITY QDa Detector, you can minimize the risk of unexpected coelutions or components and you can confirm trace components with certainty because of the analytical confidence that mass detection brings. Enhance the analytical value and productivity of each analysis, eliminating the need to run all the additional assays or time-consuming alternative techniques.

Working in synergy with optical detection, you can significantly reduce the chance that a sample component will go undetected.

The ACQUITY QDa Detector is compatible with all Waters ACQUITY UPLC®, ACQUITY UPC²®, Alliance® HPLC, and purification LC and SFC systems. The ACQUITY QDa Detector is complementary to your current Waters optical detectors including ACQUITY UPLC PDA, TUV, or FLR, or ACQUITY UPC² PDA optical detectors.

The mass spectral information combines seamlessly into the same workflow, routinely giving you more complete characterization of your separation.

Process, interpret, visualize, and compare the most complex data, and turn it into meaningful information quickly and simply. The ACQUITY QDa Detector is fully compatible with Empower Software, our industry-leading chromatography data software platform.

With integrated optical and mass detector data processing workflows, you can also interrogate mass spectral data in the same way and same workflow as you do PDA data. The ACQUITY QDa Detector is also fully compatible with MassLynx® Software and its suite of Application Managers.

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Analytical Challenges and Case Studies in Method Development for Fixed-Dose Combinations

LIVE WEBCAST: July 17, 2014 at 11:00 am EDT

Register for free at www.pharmtech.com/method_development

EVENT OVERVIEW:

Combining two or more active pharmaceutical ingredients in a single-dosage form can increase a drug's efficacy and improve patient compliance. Pharmaceutical companies are turning to these fixed-dose combinations to maximize product value and expand a product's lifecycle.

These changes in formulation affect the analytical methods used and often trigger challenges not previously considered. Typical challenges include:

- Analyzing dose form components separately or in combination
- Dose form components compatibility when in solution
- Impurity analysis on different wavelengths
- Sample preparation challenges
- Separation optimization
- Trapping column application and screening

In this webcast, experts will discuss challenges and solutions for the development of analytical methods associated with fixed-dose combinations. Case studies will demonstrate the complexities involved with analyzing these dosage forms.

Who Should Attend:

- Pharmaceutical Development Scientists, Pharmaceutical Analytical Chemists, Project Managers, Process Development Scientists, Pharmaceutical Chemists, Research and Development Scientists, Formulation Scientists, Project Managers

Key Learning Objectives:

- Understand complexities of analyzing two active ingredients at two different wavelengths and strategies that are successful.
- Gain an understanding that the chemistry in the fixed-dose combination formulation is fundamental to the development of a sound analytical approach.
- Learn how to develop and transfer methods for commercial products with complex formulations and four active pharmaceutical ingredients.

Presenters:

Gordon Marr
Associate Director
PDS Analytical Development

Yue Chen
Supervisor,
PDS Analytical Development

Maureen McLaughlin
Analytical Chemist
Patheon

Moderator:

Rita Peters
Editorial Director
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For questions, please contact Kristen Moore at kmoore@advanstar.com

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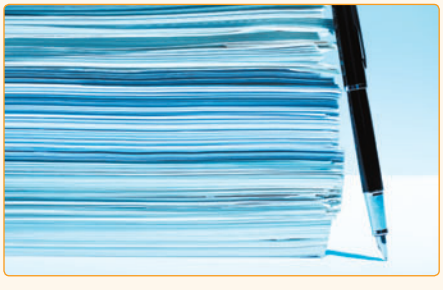

Pharmaceutical Technology and *Pharmaceutical Technology Europe* cover all aspects of pharmaceutical drug development and manufacturing, including formulation development, process development and manufacturing of active pharmaceutical ingredients (both small molecule and large molecules) and finished drug-products (solid dosage, semisolid, liquids, parenteral drugs and topical drugs), drug-delivery technologies, analytical methods development, analytical testing, quality assurance/quality control, validation and advances in pharmaceutical equipment, machinery, instrumentation, facility design and plant operations.

We are currently seeking novel research articles for our peer-reviewed journal as well as manuscripts for our special issues. For peer-reviewed papers, members of the Editorial Advisory Board of *Pharmaceutical Technology* and *Pharmaceutical Technology Europe* and other industry experts review manuscripts on technical and regulatory topics. The review process is double-blind. Manuscripts are reviewed on a rolling basis.

Our single-themed issues, which include literature reviews and tutorials, address excipients and ingredients, analytical testing, outsourcing, solid dosage and more.

Please visit our website, www.PharmTech.com/Authors, to view our full Author Guidelines. Manuscripts may be sent to Editorial Director Rita Peters at rpeters@advanstar.com.

We look forward to hearing from you.

Data Integrity

Siegfried Schmitt, Principal Consultant, PAREXEL International, discusses how to ensure data integrity.

Q. Data integrity has been making headlines recently, in response to foreign inspections by FDA and European regulatory agencies (1). Based on these reports, it appears that data integrity issues center largely on manufacturing companies in Asia. Should we conclude that these issues only concern firms already struggling to comply with basic good practices in this part of the world?

A. In general, media tend to report on the most serious violations uncovered by regulators. Often when companies find similar issues through their own internal investigations, they remain confidential and unreported. It would, therefore, be presumptuous to assume violations reported on by the press are representative of the industry as a whole.

What inspections have triggered, however, is increased attention toward potential data integrity issues lurking across the industry. Few companies would have data integrity verification activities integrated into their quality oversight programs before these examples of serious violations of healthcare regulations became public knowledge in the form of warning letters (2), consent decrees (3), or reports in the European EudraGMDP database (4).

Conscientious companies have taken these potential data integrity issues seriously by starting internal investigations, incorporating data integrity assessments into their quality assurance oversight programs, and in some cases, establishing a special data integrity office. Companies—even those in good standing with regulators—have initiated such activities regardless of existing or anticipated compliance concerns.

The question is: what have these internal investigations uncovered, if anything? The answer, surprisingly, is that they have uncovered a significant amount. Once you start studying analytical data, root cause analyses, logbooks, and any other data source, gaps are repeatedly found in data traceability and trustworthiness. A few data-related issues include: uncertainty where the data originated from and who created it (e.g., where several analysts use the same user ID and password on a set of similar instruments); which raw information produced the reported data (e.g., where a summary table reports stability data results, but all raw data on the chromatography instrument have since been deleted); and whether these are the original data (e.g., where there is no audit trail on the analytical instrument). These issues are not necessarily the result of willful malpractice, but are often caused by insufficiently controlled processes, poor documentation practices, suboptimal quality oversight, and often enough, professional ignorance.

Occasionally people do intentionally falsify data. This is unfortunate but, thankfully, still a rarity.

The following are some steps companies should take to ensure data integrity:

- Embed data integrity verification activities into internal audit processes
- Create awareness among staff so they can assist with this endeavor, and report concerns before they become full-fledged issues
- Train internal auditors to understand what to look for when detecting data integrity deficiencies
- Seek external support to assure completely unbiased, third-party investigations and/or to enhance your internal investigation program.

It should come as no surprise that companies already struggling to meet basic compliance standards are at a disadvantage when it comes to data integrity. Making data integrity a key element of a compliance approach, however, will give the company a competitive advantage. It is always better to proactively prevent issues, such as data integrity failures, to occur, than trying to remediate and resolve inspection findings. Compliance excellence makes good business sense.

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Your opinion matters.

Have a common regulatory or compliance question? Send it to shaigney@advanstar.com and it may appear in a future column.

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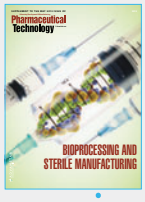

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