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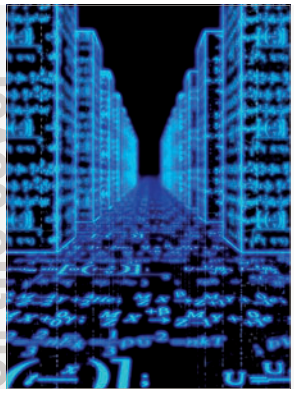

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Podcast

Kurt Nielsen, PhD, chief technology officer and senior vice-president of R&D at Catalent Pharma Solutions, discusses strategies for solubility and bioavailability enhancement of poorly water-soluble drugs.
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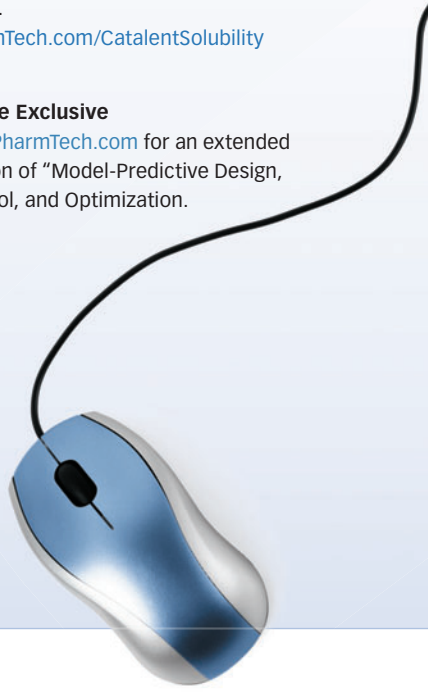

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PHARMACEUTICAL TECHNOLOGY (Print ISSN: 1543-2521, Digital ISSN: 2150-7376) is published monthly, except two issues in June, by Advanstar Communications, Inc., 131 W. First St., Duluth MN 55802-2065. Subscription rates: US and possessions — 1 year (13 issues), $70; 2 years (26 issues), $125. Canada and Mexico — 1 year, $95; 2 years, $145. All other countries 1 year, $135; 2 years, $250. International price includes air-expedited service. Single-copies (prepaid only) — US, $8; outside the US, $10. Back issues (if available): US and possessions — $21; all other countries — $25. Include an additional $6.50 per order plus $2 per additional copy for US postage and handling. If shipping outside the US, include an additional $10 per order plus $3 per additional copy. Periodicals postage paid at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to Pharmaceutical Technology, PO Box 6188, Duluth, MN 55806-6188. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A.

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Trust in the Pill Bottle

Rita Peters

The Ranbaxy settlement provides a cautionary tale for patients, FDA, and drug manufacturers.

In mid-May, Ranbaxy Laboratories Limited, India's largest pharmaceutical company, pleaded guilty to US Department of Justice felony charges relating to the manufacture and distribution of adulterated drugs made at two of the company's manufacturing facilities in India. The company agreed to pay $500 million—the largest financial penalty paid by a generic pharmaceutical company—for violations of the US Food, Drug and Cosmetic Act (FDCA) and False Claims Act (FCA).

Ranbaxy agreed to pay a criminal fine and forfeiture totaling $150 million. It will pay another $350 million to settle civil claims that taxpayers paid for substandard drugs used in programs such as Medicare and Medicaid. A Ranbaxy press release explained "a previously disclosed investigation by the US Department of Justice (DOJ) of data integrity and manufacturing processes at certain Ranbaxy facilities in India has been concluded."

"While we are disappointed by the conduct of the past that led to this investigation, we strongly believe that settling this matter now is in the best interest of all of Ranbaxy's stakeholders," Arun Sawhney, chief executive officer and managing director of Gurgaon, India-based Ranbaxy, said in the statement. "The conclusion of the DOJ investigation does not materially impact our current financial situation or performance."

Despite its confidence in the bottom line and a tagine of "Trusted Medicines. Healthier Lives." on its website, Ranbaxy USA pleaded guilty to three felony FDCA counts, and four felony counts of knowingly making material false statements to FDA, DOJ reports. The list of infractions shows problems dating to 2003. The company admitted to selling batches of adulterated drugs including Sotret, gabapentin, and ciprofloxacin; had incomplete testing records and inadequate programs to assess the stability characteristics of drugs; and had significant cGMP deviations in the manufacture of certain APIs and finished products. The company also admitted to failing to file in a timely manner required reports for batches of Sotret and gabapentin that had failed certain tests.

An investigative report by *Fortune* magazine details "long-term criminal fraud" at Ranbaxy.

DOJ reports Ranbaxy USA was aware in January 2003 that a batch of Sotret failed an accelerated dissolution stability test but continued to distribute the batch into the US for another 13 months. At various times between June and August 2007, certain batches of gabapentin were testing out-of-specification, had unknown impurities, and would not maintain their expected shelf life; the company did not notify FDA or institute a voluntary recall until October 2007.

However, the Ranbaxy and DOJ statements tell only part of the story. An investigative report by *Fortune* magazine details "long-term criminal fraud" at Ranbaxy, and FDA's response to it " … raises serious questions about whether our government can effectively safeguard a drug supply that last year was 84% generic ..." The article, based on interviews with former Ranbaxy employees, internal documents, regulators, and scientists, describes a pattern of invented data, falsified documents, a lack of testing, and ignorance and disregard of regulatory procedures (1).

The article reports that some former Ranbaxy executives and FDA inspectors with knowledge of the company's manufacturing practices would not take the company's drugs. Patients did not have insider knowledge of the manufacturing problems, but trusted the medicine and the regulatory channels; some may have paid a high price for the ineffective drugs. That's a violation of trust that the drug industry and FDA must resolve.

Reference

1. Katherine Eban, "Dirty Medicine" www.fortune.com, accessed May 20, 2013. **PT**

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

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First published April 2013. GE Healthcare Bio-Sciences Corp., 800 Centennial Ave., P.O. Box 1327, Piscataway, NJ 08855-1327 USA

HITTING THE HEADLINES

Pfizer Opens Online Pharmacy to Fight Counterfeit Medicine

Pfizer has launched a prescription-fulfillment website for Viagra (sildenafil citrate) tablets in what the company describes as an effort to combat the online sale of counterfeited medicine. Patients with a valid prescription can purchase the drug online. CVS/pharmacy will handle the back-end functions, including the authentication of all prescriptions.
PharmTech.com/PfizerOnline

GSK Announces Plans to Share Clinical Trial Data

In a commitment to transparency, GlaxoSmithKline (GSK) has outlined plans to share detailed data from its clinical trials and will establish an online system that will enable researchers to request access to anonymized patient level data.
PharmTech.com/GSKdata

USP Launches Initiative to Fight Counterfeit Drugs in Sub-Saharan Africa

The United States Pharmacopeial Convention (USP) has announced the launch of the Center for Pharmaceutical Advancement and Training (CePAT) in Accra, Ghana, part of USP's initiative to combat drug counterfeiting in sub-Saharan Africa. The center is also part of the organization's effort to promote global access to good quality medicines and is being launched as a Commitment to Action through the Clinton Global Initiative.
PharmTech.com/USPAfrica

THE MARKETPLACE

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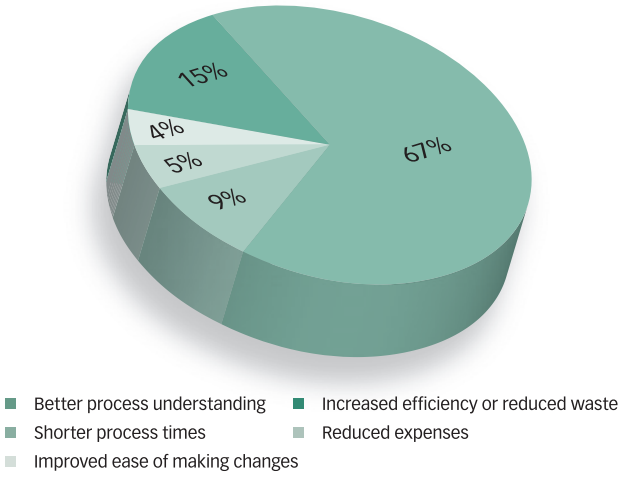

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- Big Pharma's #Manufacturing Investments in #Biologics. http://ow.ly/l3jYE

LINKEDIN DISCUSSION POINTS

What are the challenges involved in implementing a lifecycle approach to process validation?

How is the pharmaceutical industry using model-predictive design?

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ON THE BLOG

"Evidence of health outcomes is what payers want to see. As a result, biotech companies are now focusing more on demonstrating economic value, according to Ernst & Young's annual biotechnology industry report."
Adeline Siew

"At INTERPHEX 2013, I noticed a focus on equipment flexibility and ease-of-cleaning and changeover that enables manufacturing efficiency."
Jennifer Markarian

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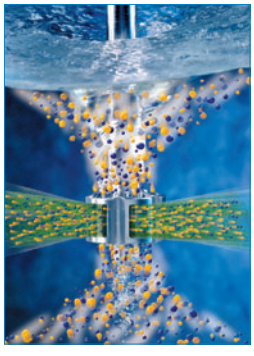

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Silverson Machines
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- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances – New Course* (September 20)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Packaging and Labeling of Drug Products – New Course* (September 20)
- Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: *Case Studies in the Manufacturing of Pharmaceutical Drug Products – New Course* (September 20)

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www.pda.org/lyophilization

- Fundamentals of Lyophilization (September 30 – October 1)
- Validation of Lyophilization (October 2 – October 3)

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REGULATORY **ROUNDUP**

Combating malaria

World Malaria Day, held on April 25, provided an opportunity to highlight several advances in biomedical research and healthcare initiatives to combat this deadly disease. One hopeful sign is success in producing a synthetic version of artemisinin, the ingredient derived from the Chinese wormwood plant that has proven effective in treating malaria. Sanofi is beginning to produce this ingredient at a plant in Italy, building on discovery of a new process developed by a collaboration of OneWorldHealth, Amyris, and the University of California, Berkeley. Initial funding from the Bill and Melinda Gates Foundation and support from PATH has led to a process that will yield 35 tons of artemisinin in 2013, using a complex photochemistry method to turn artemisinic acid into the active ingredient basic to antimalarial combination products.

There's also action to curb proliferation of fake and substandard malaria drugs. FDA is working with other government health agencies to test use of the Counterfeit Detection Device (CD-3), a handheld scanner developed by FDA scientists that can tell quickly if a product is real or counterfeit. The effectiveness of this tool in detecting bogus versions of two common malaria therapies will be piloted in Ghana, building on a United States Pharmacopeia program in that country to promote quality medicines; additional funding will come from the Skoll Global Threats Fund.

Drug spending down, prices up

Patent expirations leading to greater generic drug use continue to drive down US spending on prescription drugs, raising concerns about appropriate drug use and future development of the pharmaceutical industry. Total spending on medicines in 2012 declined by 3.5% on a real *per capita* basis according to a report from the IMS Institute for Healthcare Informatics released May 9, 2013. Outlays reached $325.8 billion, 1% less than the previous year. A main reason for the decline is that fewer patients went to the doctor and fewer prescriptions were dispensed, likely due to a rise in high-deductible health insurance policies and high coinsurance for specialty drugs.

While the drop in overall drug costs may be good news for US consumers, soaring price tags on new cancer drugs have prompted protests from oncologists. Doctors at Memorial Sloan-Kettering in New York said they won't prescribe certain medicines with more than $100,000 in annual costs that lack strong treatment benefits. Manufacturers have long claimed that they need high prices on important new products to offset the millions spent on unsuccessful research. The critics claim that industry profits are excessive, and that desperate patients should not have to shoulder the costs.

Measuring quality

FDA officials are talking more about the need for clear metrics on drug quality. But this does not mean developing "report cards" on manufacturers, says Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER). She noted at the April annual meeting of the Food and Drug Law Institute that the agency wants to develop "uniform and clear standards" for drug manufacturing for all types of medicines, with an emphasis on "clinically relevant" requirements. One aim is to ensure that senior management at companies is aware of quality problems, which she observed is often not the case.

Considering biosimilars

More manufacturers are meeting with FDA experts to discuss options and approaches for developing biosimilars, but the agency still had not received an application to test its proposed biosimilar pathway for these therapies as of late April. Manufacturers have filed 16 investigational new drug applications (INDs) for biosimilars, reported Steve Koslowski, director of CDER's Office of Biotechnology Products, at the April CMC Workshop sponsored by the Drug Information Association (DIA). The agency also has received 55 requests for meetings on biosimilars involving 11 reference products and has met with sponsors 38 times. The process has been facilitated by draft guidance published in March 2013 clarifying how sponsors should request and plan for formal meetings involving biosimilars. Koslowski clarified that a biosimilar may be proposed for fewer than all the conditions and routes of administration of the reference product, and that differences in formulation may be acceptable. There should be "no clinically meaningful differences," however, between a biosimilar and the reference product, which presents a challenge in determining "how close is close enough?"

Global regulatory standards

If a pharmaceutical manufacturer produces the same drug for international use, it should be able to work with globally accepted regulatory standards and filing requirements, says Ganapathy Mohan, executive director for global CMC pharmaceutical and devices at Merck, Sharp and Dohme. The goal should be a universally accepted set of control specifications, with common policies governing dissolution, assays, genotoxic impurities, among others. Instead, manufacturers face "a nightmare" of different filing requirements, inspection schedules, and clinical study policies, Mohan commented at the DIA CMC Workshop. Despite years of efforts to harmonize CMC requirements through the International Conference on Harmonization, regulatory authorities in key emerging markets are establishing diverse requirements for inspections, local clinical data, stability testing, and post-approval changes. Manufacturers need to demonstrate to regulatory authorities, Mohan advised, how such unique requirements generate high costs and regulatory hurdles that could block access to valuable medicines for their citizens. **PT**

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Congress Considers Legislation to Secure Drug Supply Chain

Bills to regulate drug compounding and establish a national track and trace system face political and policy differences.

Concerns about unsafe products from large pharmacy compounders, continued emergence of counterfeit medicines, and the prospect of diverse state tracking requirements for prescription drugs are spurring action on Capitol Hill. House and Senate leaders are crafting legislation to address these issues, but divergent Republican and Democrat approaches for revising FDA authority threaten to stymie timely legislative action.

Meanwhile, reports keep piling up about adulterated and unauthorized drugs. FDA recently uncovered Internet sales of a foreign version of Allergan's cosmetic treatment Botox (onbotulinumtoxinA), a sterile product, and Teva Pharmaceuticals has reported fraudulent versions of its generic Prilosec (omeprazole). Pfizer is challenging widespread Viagra (sildenafil) counterfeiting by marketing its product directly to consumers through its own website, with CVS Caremark filling the orders.

No more meningitis outbreaks

Reports of more than 50 deaths and widespread serious medical problems from fungal meningitis linked to contaminated products from a large compounder makes action most likely on legislation to curb large-scale compounding of high-risk drugs. Public outrage over the failure of state and federal agents to detect and prevent the outbreak has generated support for proposals to enhance FDA authority over compounding. Granting FDA more authority, however, will require House Republicans to shift from blasting FDA for inaction and tackle the regulatory challenges directly.

At an April 2013 hearing before the House Energy and Commerce Committee (E&C), Republicans criticized FDA commissioner Margaret Hamburg for not cracking down on the New England Compounding Center (NECC) in Massachusetts, despite NECC's long history of failed inspections and contamination problems. Democrats echoed these concerns but supported legislation that would clarify and strengthen FDA's ability to inspect and bring action against compounders, which now fall primarily under state pharmacy regulation. Hamburg noted that some compounders denied FDA inspectors access to facilities and records during a recent FDA inspection campaign, forcing the agency to seek court warrants.

FDA supports legislation that distinguishes local, traditional pharmacy compounders that prepare drugs to treat specific patients with specialized needs in response to individual prescriptions, from large compounders that produce drugs in advance of any patient-specific prescription and market drugs across state lines. States would continue to oversee traditional compounders and license compounding pharmacists, but large operators would be considered a new class of drug manufacturer and have to comply with GMPs, submit to regular FDA inspections, and report adverse events related to their products. These firms also would pay registration fees to FDA to support federal oversight and clearly label products as compounded drugs. Unlike pharmaceutical manufacturers, though, they would not need approved new drug applications (NDAs) for products they compound. FDA would develop a list of products banned from all compounding, such as complex dosage forms and most biologics.

Some of the challenges in reaching agreement among compounders, pharmacists, and state regulators were discussed at a hearing held on May 9 by the Senate Health, Education, Labor & Pensions Committee. A Senate bill that essentially supports FDA's approach for distinguishing between "traditional" compounders and "compounding manufacturers" received generally strong support. But there were questions about whether a hospital pharmacy that sends compounded products to a satellite facility in another state would fall under FDA's purview, and whether FDA should have access to records of traditional compounders to ensure that no illegal activity is taking place.

FDA has pressed for legislation to clarify its authority to regulate pharmacy compounders, which has been mired in legal debate for some 20 years, with FDA largely on the losing end. After the Supreme Court tossed out an FDA compounding regulation in 2002, the agency essentially gave up and directed its resources to other pressing issues. When signs of malfeasance at NECC appeared, "we allowed ourselves to be far too cautious due to fear of litigation that would further undermine our authority," Hamburg told the E&C panel.

FDA recently conducted dozens of inspections of large-scale firms making sterile products and has issued FDA-483 inspection reports that reveal an array of contamination and quality failures. The agency has instigated numerous product recalls, and some of the worst offenders, such as NECC, have shut down.

Some Republicans claim that FDA has sufficient power to inspect and bring charges against clearly violative compounders, and that new legislation won't help an agency that fails to protect the public health when it should do so. FDA also is wary that cracking down harder on compounders could aggravate shortages of sterile products. Moves by FDA and states to shut down large compounders could disrupt the supply of necessary drugs to hospitals and providers, Hamburg acknowledged, emphasizing the need for "tailored authorities" appropriate for compounders.

Supply-chain security

There's even more political disagreement over legislation to better secure the nation's drug supply chain by establishing a system to track pharmaceuticals from production to patient. Several senators sought to have a track-and-trace bill included in the FDA Safety and Innovation Act (FDASIA) last year, but agreed to pull it to avoid delay on the broader FDA measure. A comprehensive tracking policy in California that goes into effect in 2015, however, is spurring efforts to establish a national drug-tracking system that would supersede diverse state requirements—a key goal for manufacturers that benefit from a uniform national distribution process for medical products.

Bills crafted by House and Senate leaders generally agree on lot-level tracking, plus national standards and licensing for wholesale distributors. Both bills pre-empt state pedigree laws, with the Senate measure giving states more leeway to enact more stringent requirements.

The main point of dispute is the approach to product serialization and tracking. FDA seeks tracking to the drug unit level, with an interoperable electronic data system able to support efficient recalls and quick identification of illegal and substandard products. While most manufacturers now accept that approach, they side with distributors and pharmacists that want to start with lot-level product serialization and tracking as a more affordable and practical first step. The Senate proposal sets a 10-year schedule for establishing a unit-level tracing system, phasing in lot-level serialization over seven years, followed by adoption of product verification at the unit level. The current House bill has no provision for a future shift to unit-level tracking, a shortcoming that was roundly criticized by Democrats at an April E&C Committee hearing. At a minimum, FDA and Democrats want to delay state pre-emption until some kind of national tracking system is fully operational.

Pharmaceutical manufacturers such as Johnson & Johnson are moving to comply with the California law by applying standardized, serialized two-dimensional bar codes to packages and establishing processes to exchange serialized data with distributors and pharmacies, explained J&J Vice-President Michael Rose at the House hearing. However, these efforts would be wasted, Rose noted, if other states adopt different standards. "What we need is a clear end-game," said Rose, "where the goal posts are fixed."

E&C Chairman Fred Upton (R-Mich) initiated efforts to "mark up" the Republican-backed bill with an eye to approving legislation by August 2013. Without some provision for unit-level serialization in the not-to-distant future, though, Congress probably will reject drug-tracking legislation in 2013. **PT**

EUROPEAN
REGULATORY WATCH

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A Lifecycle Approach to Process Validation

A science- and risk-based approach to verify and demonstrate that a process operating within predefined specified parameters consistently produces material that meets all its critical quality attributes.

Pharmaceutical companies applying for marketing approval of their products in Europe are now required to provide the region's regulatory authority with documented evidence that they are using a process that consistently produces their medicines at the correct specifications and quality standards. At the moment, companies have the option of providing regulators with the details of a process validation itself or of how they intend to carry one out. However, it is likely that the requirements will become more stringent with details of process validations being demanded not only in applications for marketing authorizations but also during the post-marketing phase.

A manufacturing process should be validated before a product is launched on the market.

"Process validation is an evolving landscape with a strategy being used throughout the lifetime of a product," said Brendan Hughes, an industry participant from Bristol-Myers Squibb at the expert workshop on validation of biopharmaceutical active substances in April at the London headquarters of the European Medicines Agency, the European Union's central licensing authority.

Data collection

One of the main driving forces behind this move, which requires drug companies to provide more information on their processes, is an EMA-led policy of gathering as much data possible on the benefits risks of medicines from multiple sources including their methods of manufacture. Among the new sources of knowledge is data generated by the EU's new pharmacovigilance legislation that came into effect in July 2012. The aim is to build up an extended database on all authorized medicines, including post-marketing information on possible adverse reactions and manufacturing issues. The database complements an expanded one on GMP—called EudraGMP—containing information yielded by a new legislative requirement on GMP in the production of APIs.

The new legislative initiatives need to be "systematically utilized and further integrated to deliver continuous knowledge generation," said Peter Arlett, EMA's head of pharmacovigilance and risk management, and Tomas Salmonson, chair of the committee for medicinal products for human use (CHMP), in a joint article in the agency's latest annual report published in April. They added that "this concept of continuous knowledge generation is enabled by a lifecycle approach to data collection, and improved scientific and regulatory methods."

Lifecycle approach

With process validation, EMA wants to use, in particular, a lifecycle system for new technologies being applied in the manufacture of advanced therapies. Last year, after detailed process validation, it approved Glybera, a gene therapy for treatment of the rare inherited disorder lipoprotein lipase, developed by the small Dutch company UiQure. Glybera was the first gene therapy to be authorized by EMA and the Western world. Its production process is likely to be scrupulously monitored after the product's launch. According to EMA, the authorization paves "the way for approval of similarly complex medicines in the future, as more gene therapies for rare diseases, personalized medicines, and nanomedicines are on their way."

In a draft guideline on process validation for dosage-form medicines, issued by EMA a year ago and currently being finalized, the agency said that a manufacturing process should be validated before a product is launched on the market. However, with medicines produced by well-established technologies, details of the validation, which can be based on the traditional validation method of using studies on batch production at the pilot stage, do not have to be placed in the application dossier for authorization. Instead, the data should be held at the manufacturing site to be made available, if necessary, for inspection. With biopharmaceuticals and other "non-standard method" of production as well as specialized products such as modified-release preparation, details of the validation, which should be made with verification data at the production-scale level, should be included in the application dossier.

During the post-authorization phase, validation is seen in the guideline as a means of monitoring and evaluating the processes in a continuous manner. "It is a science- and risk-based approach to verify and demonstrate that a process operating within the predefined specified parameters consistently produces material that meets all its critical quality attributes (CQAs)," the guideline says.

After a consultation on the draft guideline, one key issue being decided by EMA is the scope of process validation, which comprises an evaluation and verification stage. It was generally agreed that continuous process verification (CPV) should be a key component of the lifecycle monitoring of pharmaceutical manufacturing. "These concepts (with continuous process verification) are new but they are acceptable approaches," said an official at the UK's medicines and healthcare products regulatory agency (MHRA).

Under their GMP obligations, pharmaceutical manufacturers should be regularly checking their production processes

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anyway. "Regardless of the nature of the medicinal product, in accordance with GMP requirements, processes, and procedures should periodically undergo critical re-evaluation, including revalidation as necessary, to ensure that they remain capable of achieving the intended results," said the MHRA official.

At the EMA's expert workshop on process validation of biopharmaceutical active substances, the difference between continuous and continued evaluation was explained in the context of GMP adherence. While continued verification is done with interruptions, continuous verification is carried out without stopping, said Kowid Ho, a member of the EMA's biologics working party (BWP), which is working on a guideline for biotechnology-derived active substances. An enabler with continued verification is GMP compliance, while with continuous verification, the enabler is quality-by-design tools such as process analytical technology (PAT) and in-line and at-line controls, added Ho, who is a biological products specialist at the French national medicines agency (ANSM). Hughes however, considered that a continued process verification can include some or all of the data sources used in the CPV procedure.

One difference between the two is that with continuous verification, the data are included in the application filing while continued verification is a basis for a prospective proposal. It may be described in the application filing but the main purpose of the data from continued verification is to show GMP compliance. The draft guideline on process validation of dosage-form medicines stresses the distinction between them. Although it says that continuous process verification depends strongly on compliance with GMP principles, its data are separate from that applying to GMP matters that are dealt with by GMP inspectors, the guideline says.

CPV is also a method that can be introduced at any time in the lifetime of a product. It can be used to revalidate commercialized products as part of the existing regulated system of post-authorization process changes, or it can be used to support an improvement program throughout the remainder of a product's lifecycle, according to the guideline.

A key aim of CPV is that it should not only be a means of verifying the validity of an original process validation but also for achieving greater knowledge of existing and new production methods. "It can be used when extensive process knowledge has (already) been gained through commercial manufacturing experience," said Ho. For the European regulators, the long-term objective behind lifetime process validation is that medicine manufacturers would achieve full understanding of their production technologies. It marks an important addition to the ways of ensuring that medicines meet the highest quality standards. **PT**

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The Meaning of Metrics

Companies can use metrics as a tool to help drive positive change and quality process improvements.

Establishing, maintaining, and interpreting meaningful metrics has become an emerging industry issue. This topic has risen to prominence based on an article (1) and a *Federal Register* notice (2) that explored the question of what types of metrics should be applied to pharmaceutical operations, giving meaningful insight to their overall quality and compliance.

There is no set requirement on what metrics a company should track to measure their overall performance. Each company should determine which metrics to track based on their operations, number of facilities they operate and where they are located, what types of products they manufacture, and what type of culture exists in their places of business.

Careful thought should be exercised when determining what to measure.

Determining which metrics to track

When establishing a metrics program, companies should evaluate numerous data input points including, but not limited to, product quality attributes, manufacturing site performance, people metrics, and quality system metrics. For product-quality metrics, companies should consider reporting on batch-specific data such as trending drug product, drug substance, and stability-test results against customer complaint rates. Indirect product quality metrics could include environmental monitoring, water trend results, and yield rates. When establishing site metrics the company could look at inspection history including internal audit findings and maintenance history such as equipment age versus defect failure rates. People metrics should consider ongoing job-specific training and education, skills and experience assessments, and employee turnover rate by job function and site. Quality systems metrics might look at change control, investigation root-cause trends, and release-testing cycle times.

The metrics chosen must be meaningful and written to provide a clear analysis of ongoing activities. It is important for operations and quality to agree on the metrics and how to report them to management to avoid overreaction to the data. It is not sufficient to simply report the data. The interpretation of the data is of crucial importance because it may include a root-cause analysis of its own.

Example metric

Let's examine a simple metric and explore the hidden unintended behavior it might encourage:

Metric: Time from completion of manufacturing to approval of batch records.

Goal: All batch records are completed in 30 days or less after manufacturing.

Realistically, not all batches will be able to be released in 30 days or less for a variety of reasons including the fact that some complex investigations into root cause may take longer to resolve than the allotted 30 days. When considering how to report this metric, the organization should consider all possible reasons for achievement or non-achievement of the goal. This includes, in essence, a root-cause analysis to interpret the meaning of the metric. Evaluation of the cause and effect relationships are necessary before determining whether or not to revise the goal. If the goal is met most of the time with a few exceptions the data might indicate the batch release system is operating as intended. If the 30-day period is exceeded on a regular basis, the organization needs to consider why the 30 days are exceeded. Some of the questions to be asked might include:

- Were there too many errors in initial submission?
- Are people unable to prioritize their work?
- Were the records too complex?

Asking and answering these questions may offer solutions that can be used to streamline the batch release process so the 30 days can be consistently achieved.

Conclusion

Careful thought and consideration should be exercised when determining what to measure, how often to measure, how to interpret and communicate the data, and what the expectation is for using the data to drive positive change. Management needs to be cognizant of the fact that whatever metrics are chosen to be reported, they must be developed, evolved, and adjusted over time to maximize their impact on driving positive change.

When choosing a metric it is important that the architects of the metric are aware of unintended consequences that may inadvertently drive negative behavior. Management attempting to incentivize achievement of the goal such as offering a financial award if the goal is achieved, for instance, may lead to inappropriate behaviors that do not address the real issue. In these cases, it is generally not the metric that will drive the behavior but rather use of behavioral rewards. Reward for achievement rather than analysis of the real underlying causes will not lead to sustainable positive change. When managed properly, metrics are an important tool to help drive positive change and quality process improvements.

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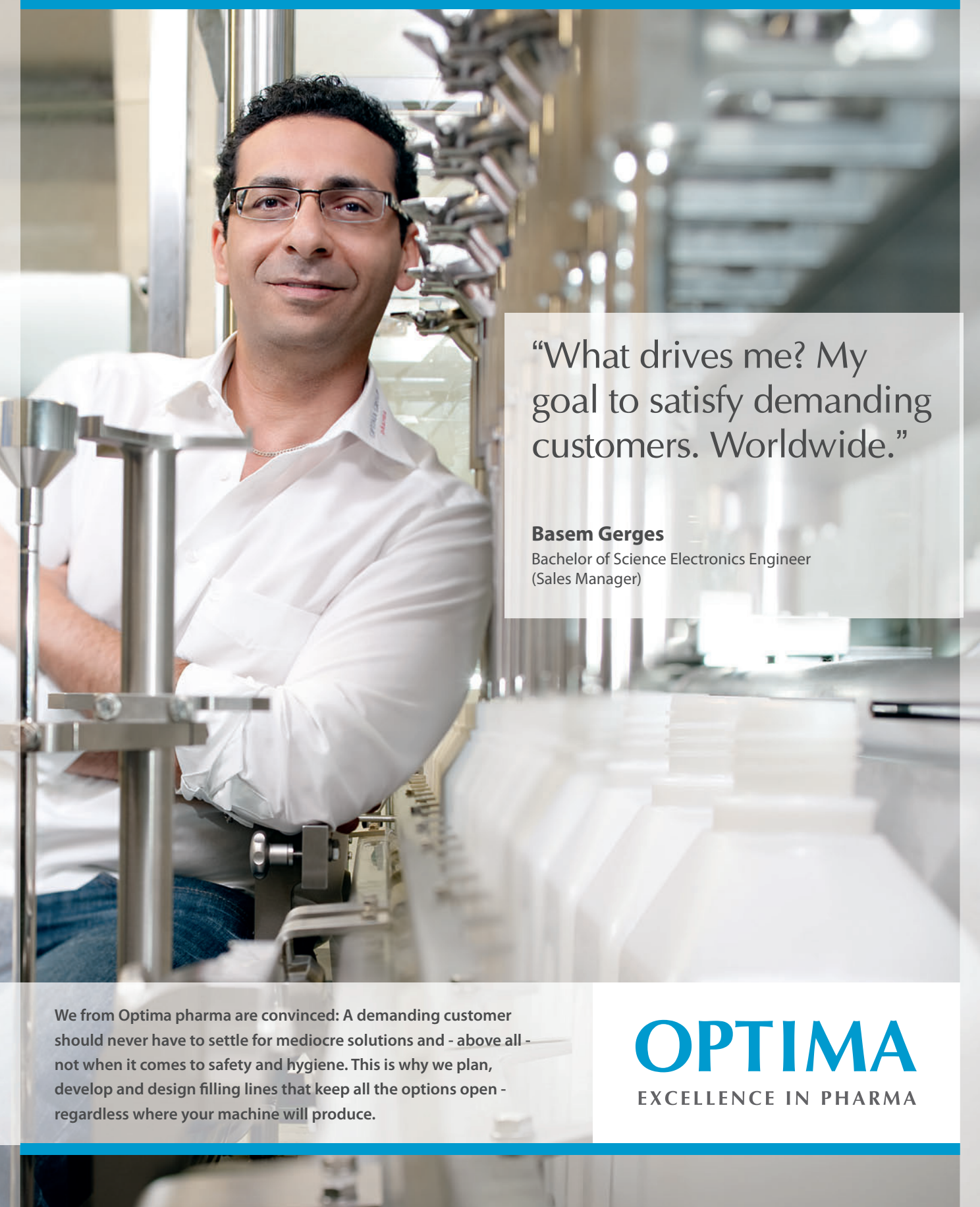

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EMERGING MARKET REPORT

Report from: Taiwan

Jane Wan

The Taiwanese government engages in regulatory science in a move to boost its pharmaceutical sector.

Taiwan is now a step closer to its goal to "promote the administration and education of pharmaceutical regulation" with the establishment of a new Center for Pharmaceutical Regulatory Science in the country by the National Cheng Kung University (NCKU). The center aims to promote pharmaceutical education and cultivate personnel training for pharmaceutical administration. Its mission also includes conducting research on pharmaceutical regulation and promoting international collaboration efforts, says Professor Yea-Huei Kao Yang, director of the center and professor of the Institute of Clinical Pharmacy and Pharmaceutical Sciences at NCKU.

Taiwan's regulatory system is comparable to that in America and Western Europe. In 2007, a health-technology assessment system was introduced for the pricing and reimbursement of new drugs. Taiwan also established its Food and Drug Administration (FDA) in January 2010 with a clear objective to establish a regulatory environment with drug-review mechanisms of international standards to run pharmaceutical affairs. Looking ahead to 2014, the agency commits to implementing the Pharmaceutical Inspection Convention Scheme (PIC/S) to help improve the quality of local medicines and upgrade production facilities to enable quicker penetration of its medicines into foreign markets.

"The setting up of a center for pharmaceutical regulatory science in Taiwan's NCKU, perhaps the first such center in Asia Pacific, mirrors the increasing importance that regulatory science is gaining among the regulatory agencies globally," says William Lee, senior director and head of regulatory strategy of the strategic drug development Asia unit at Quintiles.

Kao adds, "Its establishment is significant because it paves a clearer direction for Taiwan's pharmaceutical and healthcare industry as a whole. Overall, western and local industry players are positive in regard to this new center and believe that NCKU is taking a first step toward improving the pharmaceutical and healthcare landscape in Taiwan. The center, through its project base case studies with school professors, industry physicians, and related experts, aims to open up the communication between regulators and consumers. By its goal for transparent pharmaceutical management, the quality standard in the industry and the accessibility of information would positively improve."

According to Geeta Dhanoa, Frost and Sullivan's associate director of healthcare practice for Asia Pacific, "the preparation of the whitepaper on food and drug policy and nonprescription medicines management policy is the priority for the center, which will serve as a national platform for the government, the academia, and the industry to integrate the resources and talents." However, these initiatives are in the initial stage and the effect will be seen after the formalization of the new drug-pricing policy and reimbursement scheme. Hopefully, they would receive positive response from industry players to eliminate the regulatory hurdles so that drug registration can be improved, and to provide a conducive environment for the market participants to grow, says Dhanoa.

Center benefits

The initiatives are expected to benefit industry players. "It is expected that the approved pharmaceutical products are safer, following safety and ethical norms," Dhanoa explains. The center would also ensure that approvals for products are obtained more quickly or are manufactured in such a way as to decrease potential patient and safety problems.

"In a competitive environment, it is crucial for pharmaceutical products to reach the market in a short span of time. Hence, the

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regulatory center is expected to explore the shortest route and timeframe to put these products on the market, and support the lifecycle management of the products. This will prove to be advantageous for start-up and local firms in Taiwan," says Dhanoa.

In addition, the approval process for new drug and generic-drug manufacturing and marketing applications would include a review of the manufacturer's compliance with GMP as set by Taiwan's FDA. Based on standard operating procedures and guidelines, the regulatory center would determine whether the firm has the necessary facilities, equipment, and skills to manufacture the new drug for which it has applied for approval. Decisions regarding compliance with regulations are likely to be based on inspection of the facilities and sample analyses, which are expected to affect foreign firms entering the market.

The impact of the center's establishment can be viewed from both short- and long-term perspectives according to Lee. From a short-term perspective, one can expect an increase in cooperation and communication in academic research on pharmaceutical regulation that would promote collaboration between local regulatory agencies as well as foreign regulatory agencies and academic institutions. Such exchanges could result in a convergence of approaches to pharmaceutical regulations. Additionally, the Taiwan pharmaceutical industry could potentially see a shift in regulatory agencies taking a more science-based approach to the assessment of safety, efficacy, quality, and performance of regulated products.

Looking forward, this development may well position the Taiwanese regulatory agency as a forward-looking agency, particularly in North Asia. "As a platform to promote regulatory science within the pharmaceutical industry, the center would show the local region as well as the surrounding regions its aim to improve the overall efficiency of the industry. The movement would promote regulatory science through local and regional collaboration," Kao says. PT

—Jane Wan is a freelance writer based in Singapore.

KEY POINTS

- Taiwan's domestic market is relatively small compared to its Asian peers and the country's long-term future lies in the developed and emerging markets such as China, US, EU, and Japan. Hence, there is a need for the country's pharmaceutical sector to comply with the regulations and standard operating procedures of international market to remain competitive.
- Regulatory science is increasingly gaining importance both globally and regionally. Taiwan is perhaps the first to capitalize on this trend in the Asia Pacific region. It would not be surprising if other countries in Asia Pacific jump onto the regulatory-science bandwagon, which would bode well for the pharmaceutical industry as a whole.

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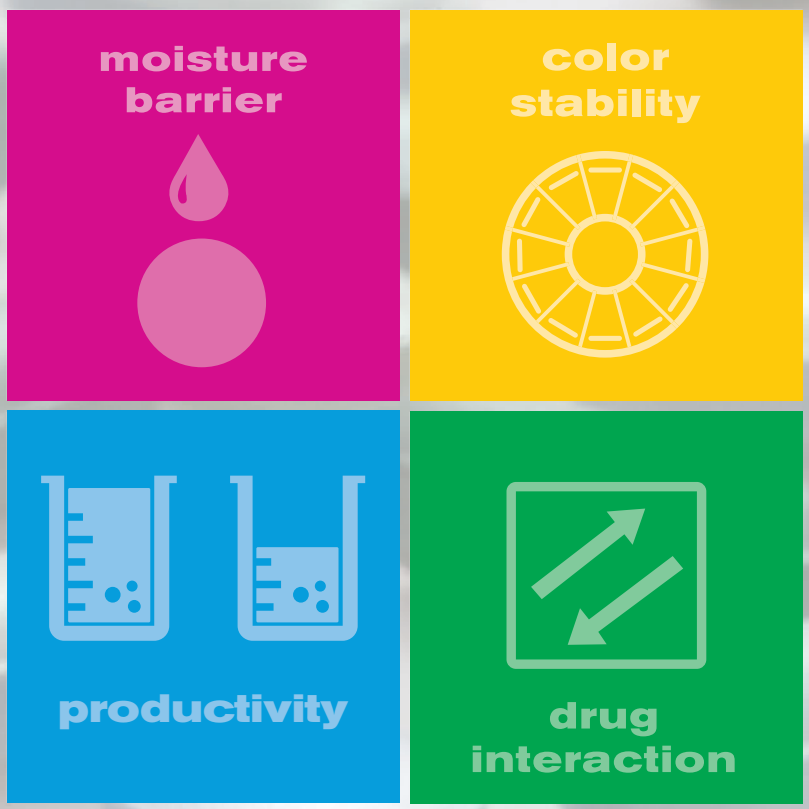

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EMERGING MARKET REPORT

Report from: Southeast Asia

Jill E. Sackman

A unique demographic and payer mix make ASEAN an increasingly attractive region.

Southeast Asia is a growing pharmaceutical market. Much like Latin America, the countries of southeast Asia, especially the members of the Association of Southeast Asian Nations (ASEAN: Brunei, Burma, Cambodia, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, and Vietnam), have taken initial steps towards seeking more harmonized regulation of pharmaceutical and medical-device industries. There are still significant differences, however, in how these markets are regulated, and these countries vary widely in their stage of development.

Southeast Asia health and pharmaceutical market overview

Healthcare has been designated a priority sector for the ASEAN countries for several years. With a population of more than 600 million, this market represents another rapidly growing emerging market. In general, the market has become more attractive in recent years as wages have risen and country governments have made healthcare sector growth a priority. Country governments are actively courting investments in the sector, and opportunities for contract manufacturing abound. Regional sales of pharmaceuticals in Asia have more than doubled from $97 billion in 2001 to $214.2 billion in 2010. It is predicted that sales will reach $386 billion by 2016 (1).

Variation between countries within the region, however, greatly impacts the opportunities for pharmaceutical companies. The Indonesian pharmaceutical industry, for example, has experienced high growth in recent years. There are a number of reasons for this. The market has a large (and growing) population (237 million according to a 2011 census), a steadily growing economy, and rising rates of chronic diseases like diabetes, obesity, and cardiovascular disease. Increasingly, we are seeing rates of chronic diseases in developing economies that have historically plagued more developed countries. Estimates for India and China, for example, suggest that these countries have the largest diabetic populations in the world (2). In addition, the Indonesian market has grown in part through the government's efforts to provide a system of universal healthcare. In its 2010 announcement, the government said that it would allow 100% foreign ownership of pharmaceutical companies. As a result, the pharmaceutical sector sales have experienced nearly twice the growth rate of gross domestic product (GDP).

In contrast, the Philippines' pharmaceutical industry has grown more slowly in recent years. The Philippines also has a large population (92 million according to its 2010 census) and is experiencing similar trends in the rate of chronic disease as Indonesia. But since the passage of the Universally Accessible Cheaper and Quality Medicines Act of 2008, the market for pharmaceuticals has noticeably changed. The law affected the market in several key ways. First, it set a maximum drug retail price that represented a 50% decrease for more than 100 drugs. It also accelerated the process for bringing generic drugs to market and disqualified drug makers from being able to patent new uses of previously existing drugs.

Other countries in the region possess unique characteristics that pharmaceutical companies should understand as well. Singapore, Brunei, Malaysia, and Thailand, for example, all have greater GDP per capita than Indonesia or the Philippines. Even though these countries contain fewer people than some of the others in the region, their demographics (e.g., higher incomes

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and increased life expectancy) may still make them attractive markets. In addition, characteristics like the fact the Singapore promotes itself as a center for medical tourism can impact the market as well.

Despite all the market potential, Asia remains a fiercely competitive region for pharmaceuticals. Part of the source of competition comes from the highly fragmented industry with literally thousands of smaller manufacturers. Many of the larger firms have been able to grow their market share partly through intensive competitive pricing (1).

Despite all the market potential, Asia remains a fiercely competitive region for pharmaceuticals.

Key regulatory considerations

In terms of regulation, the ASEAN countries are becoming more synchronized in the regulatory sphere. The ASEAN Leaders have resolved to form the ASEAN Economic Community (AEC) by 2015. The goal of the AEC is to establish ASEAN as a single market and production base. Tariffs will be eliminated and other barriers between the countries will be phased out. Work on harmonizing standards began in 1997, with pharmaceuticals, medical devices, and health supplements earmarked as priorities. Specifically, ASEAN leaders have agreed to mutual recognition of inspections of medicinal-products manufacturers, including post-market assessments. ASEAN has required the filing of an ASEAN Common Technology Dossier (ACTD) as the only regulatory filing required for pharmaceutical companies to gain approval of their drugs in the 10-member ASEAN states starting in 2012. In general, this standardization should reduce complexity for manufacturers interested in expanding into this region. Harmonization of standards will help member countries to lower costs and increase the quality and availability of medicines in the region. It also formulates rules for importing medicines to ensure quality drugs for the region. Recalls or product alerts in one country will be applicable for all the member nations.

Pharmacovigilance (PV) in Asia is evolving, as the region becomes one of the largest players in the pharmaceutical market. With increased numbers of clinical trials occurring in China, India, and the ASEAN region, the importance of managing adverse drug events/adverse drug reactions (ADEs/ADRs) is gaining recognition. There are a number of challenges that manufacturers will face with regard to developing a PV plan in ASEAN. These challenges include cultural variation in medical practice (Western vs. traditional), lack of PV expertise, lack of human and financial resources in regional regulatory agencies, few robust PV regulations, hesitation on the part of healthcare professionals to report adverse data, drug counterfeiting, and variable quality in drug manufacturing.

Some ASEAN countries have reasonably structured PV systems. In Singapore, for example, the Vigilance Branch of Health Sciences Authority employs a number of post-marketing risk assessment approaches to ensure the continued safe use of medical products. These include mandatory reporting from pharmaceutical manufacturers, spontaneous reporting from health professionals, literature reviews, and the exchange of regulatory information with other national drug regulatory bodies.

Many regulators in Southeast Asia are in the process of revising their existing regulations. There is also an ongoing collaboration across the region regarding harmonization and enhancement of drug safety as part of ASEAN.

In-region considerations

Other healthcare access considerations include country-specific items like the government's role in overall health spending. Singapore, for example, has rejected the idea of a generous welfare system, but does fund free medical care at government hospitals for the needy, and has created a universal health system characterized by medical savings accounts. While this system is supported by subsidies, no healthcare services in Singapore are provided to patients free of charge; the out-of-pocket expenses act as a deterrent from seeking out unnecessary services. Just less than half the hospitals in Singapore are government run and tend to be less expensive for patients than their private equivalents.

Other countries in the region such as Thailand have funded largely government-run programs to achieve near-universal health coverage for years, and other countries (e.g., Vietnam) are looking to employ some of the same tactics. Understanding the payer mix and the challenges facing each of these payers will be crucial to understanding the market opportunities in each of these markets.

In contrast, many of Indonesia's more than 250 million residents find even minimal healthcare inaccessible. Access to a physician or other healthcare professionals across Indonesia's 6000 inhabited islands varies greatly. While larger cities generally offer a range of medical services, in remote areas such as the province of Papua, it can take days to reach medical care.

Implications for successful market entry and in-region partnering

Under the ASEAN Economic Community (AEC), a single regional common market of countries will be created in 2015. The regional objective is to create a highly competitive market of more than 600 million people with free flow of goods, services, investment capital, and skilled labor. This shift will also include reductions in tariffs and regulatory and administrative procedures, all elements that should stimulate pharmaceutical market growth.

The eight Asian countries that are part of the ASEAN region represent a market that has historically generated relatively little industry or investor interest, but this situation is changing. Diverse influences from deregulation and better trade links to improved medical access and the rise of medical tourism are resulting in a market with an increasingly important global role to play.

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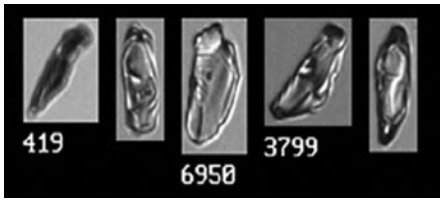

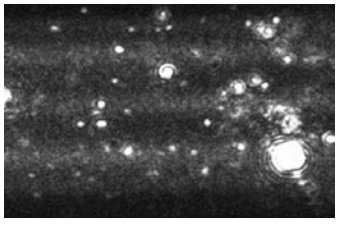

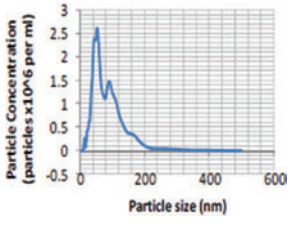

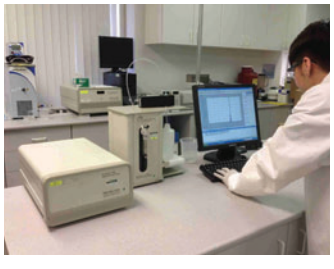

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As the single common market develops, specific implications for the pharmaceutical industry have emerged:

- Regulatory capacity in many ASEAN nations is constrained by human and financial resources requiring pharmaceutical companies to invest in developing in-region capabilities.
- Gaps often exist between written regulatory guidance and actual enforcement throughout the region, again reflecting the gap in human and financial investment.
- All ASEAN countries are net importers of pharmaceuticals (with the exception of Singapore) due to lack of investment in R&D capacity and capabilities (versus regulatory framework).
- New, harmonized drug regulatory frameworks reduce administrative barriers and encourage research and development of drugs and vaccines.

Additionally, as the healthcare sector has an immediate impact on the pharmaceutical sector, shifts in healthcare policy have enormous implications for the industry. Health insurance payment and infrastructure are relatively new and vary greatly among the ASEAN countries. In many countries, the majority of the population pays out-of-pocket for drugs and health services. And even in countries with health insurance infrastructure, there are limited resources available, so high drug prices are largely unsustainable.

Moving forward in Southeast Asia

There are many opportunities for pharmaceutical companies looking to expand in Southeast Asia. As regulation across the region becomes more harmonized and complexity decreases against a backdrop of largely sustained economic growth, the ASEAN region looks increasingly attractive. Understanding the unique demographic and payer mix of each country will be crucial to move forward and take advantage of the opportunities presented in this region.

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Using Model-Predictive Design in Solid-Dosage Manufacturing Processes

Jennifer Markarian

Models and modeling software gain a foothold in solid-dosage manufacturing process design.

Using model-predictive design to define, predict, and control a process is well-established in many industries, and is beginning to take hold in pharmaceutical process development and manufacturing. Modeling software helps developers to model unit operations and, in some cases, an entire continuous process.

Model-predictive design includes a hierarchy of different approaches, explains Bernhardt Trout, PhD, director of the Novartis–Massachusetts Institute of Technology (MIT) Center for Continuous Manufacturing (CCM) and professor in the Department of Chemical Engineering at MIT. The most basic approach is the use of linear univariate models (e.g., parameterized from a linear design of experiments). A more complex approach is multivariate analysis, followed by mechanistic modeling; the ultimate approach is analysis of first principles (e.g., conservation of mass and energy).

The pharmaceutical industry needs to move beyond statistical models, says Fernando Muzzio, PhD, director of the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) and professor in the Department of Chemical and Biochemical Engineering at Rutgers University. "Models based on first principles allow you to achieve a greater level of understanding and thus extrapolate outside of the area defined by the statistical models," explains Muzzio, who further discusses modeling tools in an article in this issue (see page 40).

Generating the level of knowledge necessary to build a model, whether it be statistically or mechanistically based, helps to speed development and mitigate risks during product development, scale-up, and commercial manufacture, adds Howard Stamato, associate director in the Portfolio Enabling Technology Group of Drug Product Science and Technology at Bristol-Myers Squibb. He adds that in those cases where the model can be used in closed-loop control, there are significant advantages for both efficiency and quality of the final product.

Much progress has already been made in employing models in the pharmaceutical industry, driven in part by advances in process analytical technology (PAT). "Advances in computing power and analytical methods, including PAT, have broadened what can feasibly be measured and subsequently modeled," says Stamato. "These advances allow models to be built with reasonable resource commitments and much higher accuracy than previously possible," he adds. In the solid-dosage drug-product manufacturing arena, modeling work has been performed, for example, in scale-up of fluidized-bed processing using computational fluid dynamics (CFD) (1) and in tablet coating using mechanistic models (2) and discrete element modeling (DEM) (3).

Models for continuous, plant-wide solid-dosage processes have also been developed (4–5). The Novartis–MIT CCM, for example, constructed a functioning prototype of an end-to-end continuous manufacturing line that forms coated tablets directly from API and, in late 2012, finished integrating the process with a control system that used models to simulate the entire process. Models for the individual unit operations are described by first principles, such as material balances, energy balances, and chemical kinetics, notes Richard Braatz, the Edwin R. Gilliland Professor of Chemical Engineering at MIT. "An advantage of first-principles models is that you can build a predictive model with less data. Statistical models tend to have poor extrapolation outside of the data range," explains Braatz. MIT used modeling software to connect the individual units and then tuned the process controllers by running simulations of the process as a whole. "Without a model of the process, we would not have been able to complete the project in an appropriate time because it would have taken too much trial and error to tune the controllers," says Braatz, who notes that when starting up a continuous process it is desirable to quickly reach steady-state operations to avoid producing out-of-specification material.

Modeling software

Modeling software tools are available to perform various computer-aided engineering tasks in development and manufacturing in various process industries, including pharmaceutical manufacturing. Models and modeling software are well established in API-production operations, such as solvent selection, crystallization, and separation, for both batch and continuous manufacturing processes, comments Jonathan Kadane, director of industry marketing for Pharmaceuticals/Life Sciences at AspenTech. Modeling for solid-dosage pharmaceutical processes is less mature. Bristol-Myers Squibb's Stamato comments, "The behavior of solids from a surface energy, flow, and compaction perspective is still difficult to characterize.

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Better understanding of the behavior of solids would help to build more computationally manageable and accurate models." AspenTech's solids-modeling capabilities, acquired through SolidSim in 2012, model specific, solids-handling unit operations (e.g., screens, dryers, and cyclones). Although this technology is, to date, primarily targeted for chemical process industries, the early-users group includes pharmaceutical companies, notes Kadane.

Modeling software can be used in all stages of pharmaceutical production, from R&D through to quality control and manufacturing, notes Michael Doyle, principal scientist and marketing director, Materials Science Segment, at software-provider Accelrys. Process designers can use software to understand excipient–API interactions or optimize mixer speeds, for example. Process-centric software captures numeric inputs about the process (e.g., formulation data, PAT sensor data) and feeds this into predictive models that allow process developers to evaluate "what if" questions, explains Doyle.

CFD software can be used to model common operations, such as scaling up a mixing tank, and for more complex operations, such as three-dimensional modeling of a fluidized bed (e.g., tablet coater), explains Kristian Debus, director of Life Science at CD-adapco.

Some particle flow can be modeled with CFD alone, but to capture more detail about particle behavior (i.e., how particles interact with each other, the surrounding walls and equipment parts, and air flow), developers use discrete element modeling (DEM) software. "DEM tracks the interaction between every particle in a numerically efficient manner, modeling contact forces and energy transfer due to collision and heat transfer between particles," explains Debus. DEM has been used extensively to model mixing and coating, and there is now increased interest in using DEM for granulation and compaction, says Richard LaRoche, PhD, vice-president of Engineering at DEM Solutions.

Another type of CFD is multiphase fluid flow (e.g., volume-of-fluid method). This method can range in complexity from nonmixing to phase mixing, which allows modeling of suspensions, for example. Models can also be done in steady state or in real time (i.e., transient state). As complexity increases, so does the computation time and expense. When choosing how to model a process, companies must balance the accuracy needed with the computational expense that will incur.

In the past, computational capabilities have limited applications to laboratory and pilot scales, says DEM Solutions' LaRoche. This work, however, can be used to help devise scale up-rules for process engineers. The company recently added the capability of running DEM on large, high-performance computing and shared-memory systems, which will enable production-scale modeling.

Another type of software uses flowsheet modeling to describe individual unit operations and provide mechanisms for exchanging data between these unit operations. This method combines techniques, such as DEM, CFD, and population balance modeling, and can be used, for example, in solid-dosage process development to predict what type of process (i.e., wet granulation, dry granulation, or roller compaction) should be targeted or to predict how upstream API properties affect downstream tablet production (6), adds Douglas Hausner, associate director for industrial relations and business development at C-SOPS.

Looking ahead

An increasing use of modeling in the pharmaceutical industry is being driven both by the FDA mandate to better control the manufacturing process using quality by design and PAT and by the imperative of reducing drug-product development costs and speeding the development process, explains Doyle. A greater focus on efficiency, agrees Kadane, will push the industry toward more process modeling. Modeling the process first, before running experiments, saves time and money because simulated experiments are faster and cheaper than laboratory or pilot-plant experiments. In reality, however, model development and experimental development are run in parallel and correlated with each other, adds Debus. When used together, the process is better understood and error is reduced.

The ultimate goal is to use predictive models to interpret, understand, and control the pharmaceutical process, adds Doyle. Achieving this state would improve consistency and reduce out-of-specification product.

The real power of modeling software for the pharmaceutical industry, says Debus, is in modeling an entire continuous manufacturing process, including three-dimensional models (e.g., multiphase fluid flow, DEM) of the unit operations and one-dimensional models (e.g., fluid flow through a pipe) of the transfer from one unit to another. Modeling the process as a whole allows advanced process control, in which a parameter change in one unit operation is accounted for in other parts of the process as it affects other unit operations.

Most big pharma companies are using CFD, mostly at a basic level, and smaller pharma companies are just getting started with CFD, comments Debus. Process industries (such as chemical), manufacturing industries (such as automotive), and industries in which flow and particle interaction are crucial (such as aerospace and nuclear), have advanced the use of modeling. The task at hand in the pharmaceutical industry is for all parties (i.e., software and equipment vendors, pharmaceutical producers, and academia) to work together using and improving these tools to better understand pharmaceutical processes.

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How is the pharmaceutical industry using model-predictive design?

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Model-Predictive Design, Control, and Optimization

Fernando Muzzio, Ravendra Singh, Anwesha Chaudhury, Amanda Rogers, Rohit Ramachandran, and Marianthi Ierapetritou

Applying model-predictive methods and a continuous process-control framework to continuous tablet-manufacturing processes.

Currently, there is a high level of interest in the pharmaceutical industry in continuous-manufacturing strategies, integrated with online-monitoring tools, that are designed, optimized, and controlled using advanced, model-predictive systems. These strategies can accelerate the full implementation of the quality-by-design (QbD) paradigm for the next generation of pharmaceutical products. In addition to its flexibility and time- and cost-saving features, continuous manufacturing is intrinsically steady and therefore easily amenable to model predictive design, optimization, and control methods. These methods have proven to be effective approaches to improve operational efficiency and have been widely used in various process industries. Excitingly, in the pharmaceutical industry, the application of the model-predictive design, optimization, and control is virgin territory, wide open to researchers and technology providers.

Using modeling methods

Goals of recent QbD efforts include development of the scientific mechanistic understanding of a wide range of processes; harmonization of processes and equipment; development of technologies to perform online measurements of critical material properties during processing; performance of real-time control and optimization; minimization of the need for empirical experimentation and, finally, exploration of process flexibility via design space (1). In many cases, these goals can be achieved effectively and efficiently by the joint application of designed experiments and modeling tools such as discrete element modeling (DEM), computational fluid dynamics (CFD), statistical models, and population balance models (PBM). DEM and CFD are mechanistic in nature and can effectively capture the motion of particles within equipment or their interaction with a stream of fluid. The DEM approach has been implemented in various pharmaceutically relevant unit operations, such as blending, granulation, and coating (2). The application of CFD has been observed in unit operations, such as mixing, granulation, and crystallization (3). Statistical models, such as response-surface methodologies, have been largely used to determine design space and to a lesser extent for optimization (4). PBMs (hyperbolic partial differential equations representing a mesoscopic framework) have also been widely implemented on particle-based unit operations, such as granulation, crystallization, and mixing (5).

An additional modeling tool is the use of response-surface models, which are typically developed using data from designed experiments and subsequently used to select process optima and to design control algorithms. While the data-driven models used in this application are largely empirical and do not require a mechanistic understanding of the processes to which they are applied, they are invaluable as tools to aid understanding of the relative importance of process and formulation variables and thus help narrow down the scope of work required to advance process understanding.

These tools are increasingly becoming common components of the pharmaceutical process-design toolbox. They have spread from academia to the largest pharmaceutical companies, many of which have formed process-modeling groups in which researchers are using these tools to design and optimize processes *in silico* prior to expensive equipment acquisition or to reduce the complexity of designed experiments.

To date, efforts have been piecemeal and typically have focused on individual process components. The emergence of continuous manufacturing as a central focus of attention, however, is now motivating the need to develop modeling frameworks capable of simulating all process components simultaneously, using a variety of tools suited for each specific process. The flowsheet framework meets this need.

Flowsheet modeling

The continuous manufacturing of drugs can be achieved using various routes: direct compaction (DC), roller compaction (dry granulation or DG), or wet granulation (WG), depending on the starting and desired end properties of the formulation. DC is the simplest of the processes mentioned above while DG and WG improve flowability characteristics to prevent ingredient segregation and to increase density. DC (6), DG (7), and WG (8) routes have been explored using model-predictive flowsheet methodologies. Application of advanced modeling techniques for optimization and control (9, 10) on the overall flowsheet instead of the individual unit operations would enable efficient operation of the continuous process.

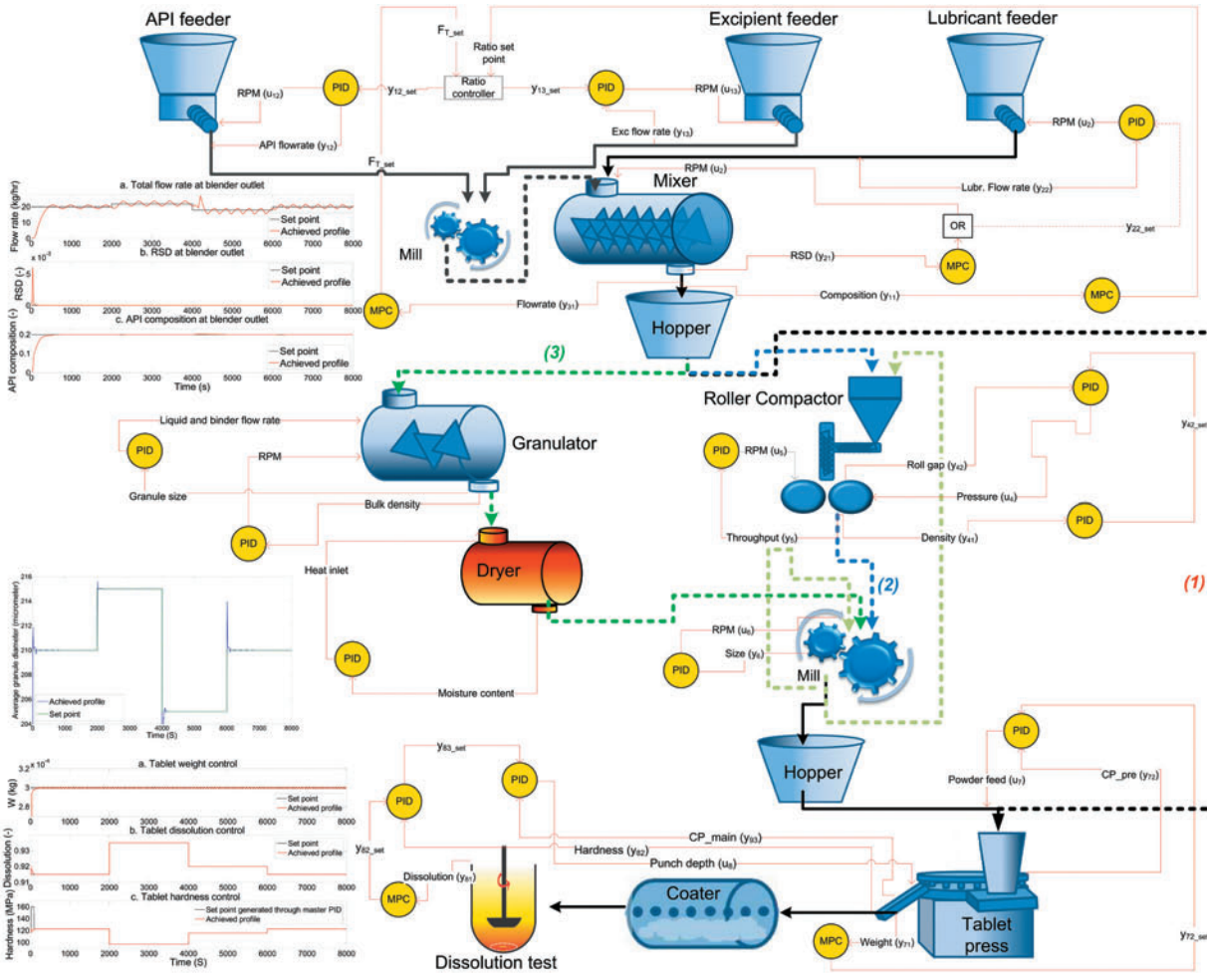
Challenges associated with developing robust and reliable flowsheet models for solids' processes include:

- Characterization of all unit operations
- Development of models that describe their constituent mechanisms
- Performance of experimental studies for the data acquisition of multi-dimensional key particle properties

FIGURE IS COURTESY OF THE AUTHORS.

The authors are from the Engineering Research Center for Structured Organic Particulate Systems (ERC-SOPS), Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA.

Figure 1: Flexible continuous tablet manufacturing process with (1) direct compaction, (2) roller compaction, and (3) wet granulation.



- Identification of all the possible manipulated and controlled variables and their interactions (9, 10)
- Integration of process design and control to identify globally valid operating conditions.

Extensive research is ongoing to identify and develop predictive models for all the unit operations involved in the continuous tablet-manufacturing process. For integrating the various unit operations into a flowsheet, it is crucial to correctly identify the critical connecting properties that communicate across units (9). Simulating the overall flowsheet, the variations in the key properties can also be tracked during the transient states involving process start-up, perturbation propagation, dynamic response to change in settings due to control actions, and process shutdown. Furthermore, through the implementation of various operating scenarios, the flowsheet model can be used for the assessment of different process alternatives (so far achieved by expensive laboratory tests), which are then scaled up to the desired plant size. The developed and validated flowsheet-simulation system can also be used for operator training, since any sequences in operating schedules can be performed virtually and analyzed through a computer screen. Using information obtained from the flowsheet models for plant implementation is the next challenge. Incorporating control systems in the actual plant is a crucial task needed for efficient operation and minimal variation from the setpoint values.

Of particular interest from a regulatory perspective is the use of integrated flowsheet models to enable identification of the propagation of noise or upsets in a particular unit operation through the entire continuous line (8, 10). This issue is directly relevant to the assessment of robustness and reliability of the continuous manufacturing system. Process optimization can be achieved by implementing optimization algorithms on the overall integrated model. **Figure 1** shows a flowsheet model (simulated in gPROMS, Process Systems Enterprise) of a flexible, continuous, tablet-manufacturing process together with the implemented control system.

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Measuring Tablet Hardness: A Primer

Eric Chiang

Crushing, fracturing, and bending tests quantify hardness.

Solid tablets are perhaps the most commonly used dosage form for pharmaceuticals. Tablet hardness serves both as a criterion to guide product development and as a quality-control specification. Tablets should not be too hard or too soft. An extremely hard tablet could indicate excessive bonding potential between active ingredients and excipients, which can prevent proper dissolution of the tablet needed for an accurate dosage. By the same token, a softer tablet could be a result of weak bonding and may lead to premature disintegration when ingested by the patient. A soft tablet could also chip or break during processing stages in manufacturing, such as coating and packaging.

Knowing the mechanical properties of a solid-dose tablet can provide valuable information for optimizing material constituents and the manufacturing process. The types of binders used, the nature of the active ingredient(s), and the composition of the ingredient(s) in the tablet will affect the hardness of the tablet; the tablet press speed, granulation flow, and air in the powder can also potentially affect tablet hardness (1). These factors must be controlled during production and verified after manufacture. As the production-to-market timeline of pharmaceutical products becomes tighter, it is essential to efficiently and effectively quantify the critical properties that will affect product development and performance.

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Methods for measuring the mechanical strength of a tablet include crushing, fracturing, and bending tests (2).

Crush test

The crush test is usually performed on a round tablet standing on its rim, or, for a capsule-like tablet, parallel to the longest axis. This test is sometimes known as a diametrical compression test. The test sample is placed on a base table and compressed against a flat surface cylindrical probe as shown in **Figure 1** (CT3 Analyzer, Brookfield Engineering). The cylindrical probe surface, which is larger than the test sample, is moved down to crush the tablet at a constant speed, and the force applied to crush the tablet is measured (see **Figure 2**). The load-force values obtained will depend on the construction and size of the tablet. **Figure 3** shows a typical plot of force load (g) vs. time (s) as the test progresses (TexturePro CT software program, Brookfield Engineering). The highest point on the graph, peak load, is the load required by the analyzer to break the tablet. This point also indicates the tablet's maximum strength before breaking. Subsequent smaller peaks suggest that the test tablet was not fully broken down at the maximum load. The smaller peaks represent continuous fracturing of the tablet until full disintegration.

Fracture test

The fracture test is accomplished by driving a smaller hemispherical ball probe into the flat surface of a solid tablet (see **Figure 4**). A suitable probe deformation distance must be chosen to avoid base effect, which is the external influence of the

Figure 1: Crush test on tablet (CT3 Analyzer, Brookfield Engineering).

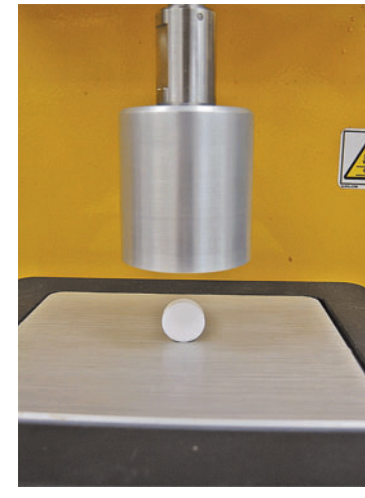
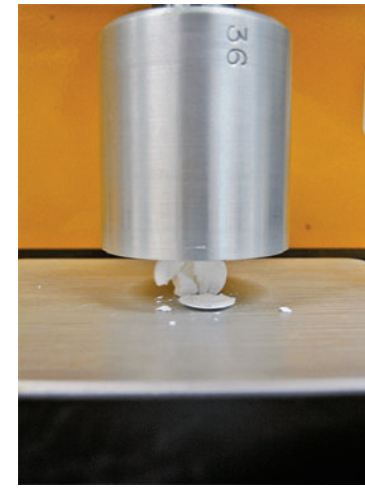


Figure 2: Cylinder probe fractures tablet in crush test (CT3 Analyzer, Brookfield Engineering).



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substrate surface on which the tablet is placed. Base effect is caused by compression of a thin sample against the test bed of the analyzer instrument, which inadvertently renders incorrect results. A deformation distance of not more than 60% of the sample height is usually enough for the ball probe to fracture the tablet without causing base effect. The maximum strength of a tablet before breaking is the peak load on the graph plot (see **Figure 5**). The recorded force applied to fracture the tablet is useful for determining mechanical properties, such as Young's modulus and tensile strength. Young's modulus, which is the ratio of stress over strain deformation ($E = \sigma/\varepsilon$), describes the stiffness and toughness of a material.

Bending test

Another common fracture test on tablets is the snap or bending test. This test is common for an oval tablet shaped like a capsule (i.e., caplet) as well as on a fairly large round tablet. The test is performed with a three-point bend fixture; the tablet is supported at either end and deformed in its center with a knife-like probe, causing it to fracture and break at its weakest point (see **Figure 6**). To ensure comparability of results, the tablet's orientation in the fixture must be standardized, preferably in a manner that is most readily and easily reproduced by operators (e.g., align the score line of the tablet with the probe blade). In the plot in **Figure 7**, the peak load (Y-axis) indicates the tablet hardness; harder tablets will give a higher peak load. The distance to peak load (X-axis) is an indication of the elasticity of the test sample. Brittle samples (such as solid-dose tablets) will have a shorter distance or time at failure hardness compared to elastic samples.

Conclusion

These tablet hardness tests provide a meaningful picture as to the amount of force required to fracture the solid-dose tablet. This knowledge will be useful in gauging the tablet's resistance to damage that might occur during production handling, packaging, and storage. Based on this testing, guidelines for acceptable hardness values can be established. The test is also useful for quantifying the internal bonding strength of powder, which will help to achieve compatibility of formulation with performance specifications. Tests can also be used to enhance the production evaluation of tablet consistency between different batches, shifts, and facilities.

Figure 3: Graph of tablet-crush test.

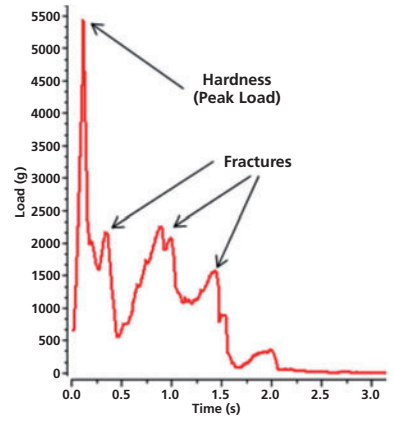


Figure 4: Fracture test on tablet (CT3 Analyzer, Brookfield Engineering).

Figure 5: Graph of tablet-fracture test.

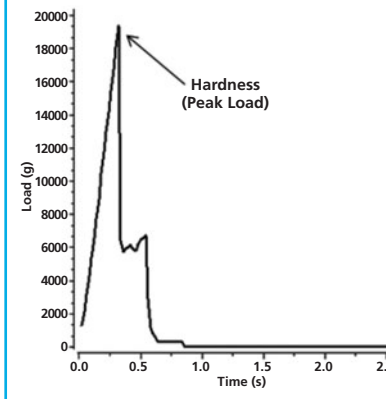
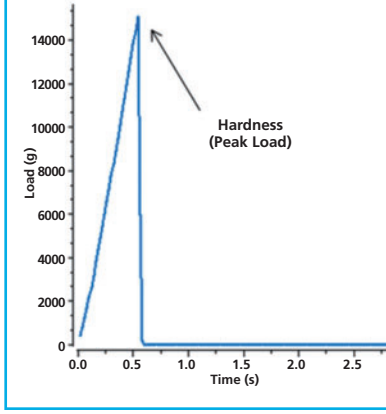


Figure 6: A blade splits the tablet in a bending test (CT3 Analyzer, Brookfield Engineering).

Figure 7: Graph of tablet-bending test.



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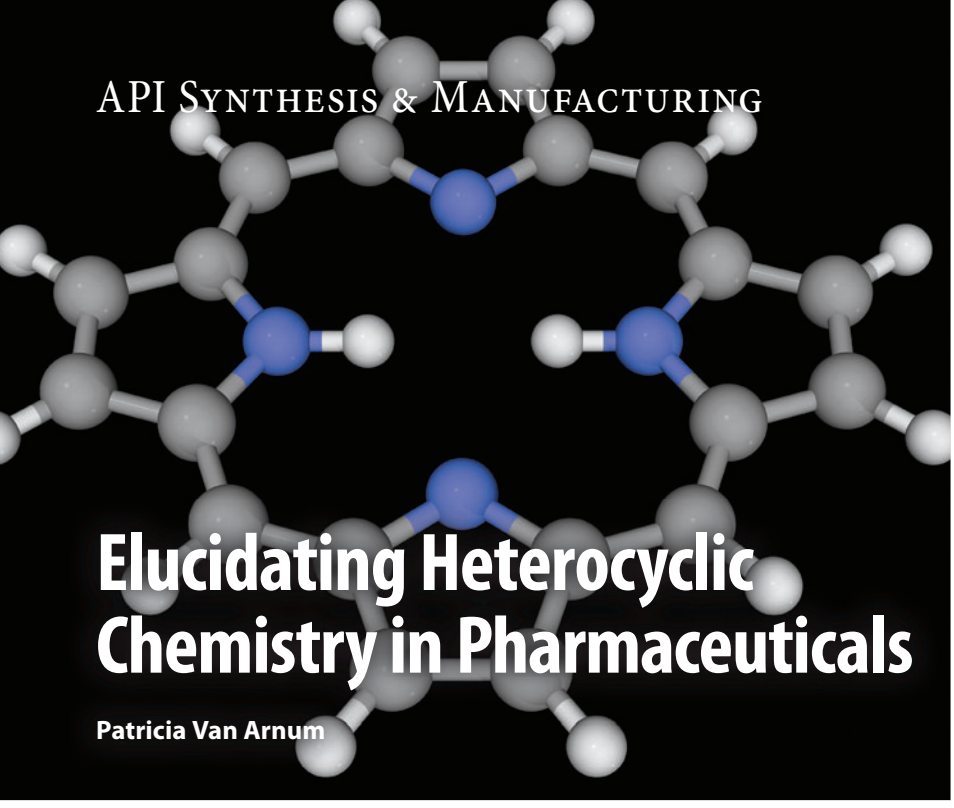
2. J.M. Newton, G. Alderborn, and C. Nystrom, *Pow. Technol.* 72 (1) 97-99 (1992). **PT**

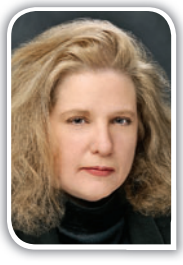


Elucidating Heterocyclic Chemistry in Pharmaceuticals

Patricia Van Arnum

Researchers at the Scripps Research Institute advance heterocyclic chemistry through new reagents and reaction-tracking techniques.

Heterocyclic compounds play an important role in medicinal chemistry and drug synthesis. Like any important functional class of compounds, developments that facilitate their production or elucidate their reaction mechanisms are significant for process chemists in the pharmaceutical industry. In two separate developments, researchers at The Scripps Research Institute (TSRI) in La Jolla, California recently reported on the use of zinc sulfinates as reagents for the direct chemical functionalization of nitrogen-based heterocycles and on reaction-tracking tools to better elucidate copper-catalyzed reactions in making triazoles.



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A toolkit for synthesizing heterocycles

In the first development, scientists at TSRI developed a set of chemical tools to simplify the synthesis of nitrogen-based heterocycles through more time- and cost-efficient chemical modifications of these compounds. In their work, the researchers pointed out that although advances in transition-metal-mediated cross-coupling have simplified the synthesis of such heterocycles, the carbon–hydrogen functionalization of medicinally important heterocycles that does not rely on prefunctionalized starting materials was an area requiring further research (1). Although the properties of heterocycles, such as their aqueous solubility and their ability to act as ligands, are desirable for biological applications, these properties also make such heterocycles challenging as substrates for direct chemical functionalization (1). To address that problem, the researchers used zinc sulfinate salts to transfer alkyl radicals to heterocycles, thereby allowing for the mild (i.e., moderate temperature, 50 °C or less), direct, and simple formation of carbon–carbon bonds while reacting in a complementary fashion to other carbon–hydrogen functionalization methods (i.e., Minisci, borono-Minisci, electrophilic aromatic substitution, transition-metal-mediated carbon–hydrogen insertion, and carbon–hydrogen deprotonation) (1). The researchers prepared a toolkit of these reagents and studied their reactivity across a range of heterocycles (natural products, drugs, and building blocks) without recourse to protecting-group chemistry. The reagents could be used in tandem in a single pot in the presence of water and air (1).

"Feedback from companies that have started to use this toolkit indicates that it solves a real problem for them by boosting their chemists' productivity and by expanding the realm of compounds that they can feasibly generate," said Phil S. Baran, PhD, a professor in the Department of Chemistry and a member of the Skaggs Institute for Chemical Biology at TSRI who led the study, in a Nov. 28, 2012 TSRI press release. The resistance of nitrogen heterocycles to modification by traditional techniques has slowed drug discovery and has put potential modifications out of reach, notes TSRI.

The genesis behind the toolkit began with the goal for a more a simplified approach. "The ideal for discovery chemists would be a method that works in water, in an open flask, [and] with procedures that are simple enough to be automated," said Baran. His group's previous work in synthesizing a natural product heterocycle, palau'amine, a toxin made by sea sponges in the Western Pacific that has shown anticancer, antibacterial and antifungal pharmaceutical promise, was a helpful beginning.

"As we developed an understanding of how that compound reacts, we recognized that it might help us solve this larger problem that discovery chemists face," said Baran in the release. In that synthesis, palau'amine was made by a route featuring highly chemoselective transformations, cascade reactions, and a transannular cyclization to produce the *trans*-5,5 ring junction (2) and led the researchers to examine reagents that would modify heterocycles directly.

LAGUNA DESIGN/GETTY IMAGES

Although direct methods exist, they often require extreme temperatures as well as expensive and hazardous reagents. During 2010 and 2011, Baran's laboratory experimented with several comparatively safe chemical reagents that work in mild conditions to make commonly desired heterocycle modifications, such as the addition of a difluoromethyl group, according to the TSRI 2012 release. One of these new reagents, a zinc dialkylsulfinate salt (DFMS), which was designed to transfer the difluoromethyl group, turned out to work particularly well. "We quickly realized that we might be able to make related zinc sulfinate salts that would attach other functional groups to heterocycles," Baran said.

In their recent work, Baran and his team developed an initial toolkit consisting of 10 of these zinc-based salts, each of which attaches a different functional group to a heterocycle framework. "We selected these groups because they are commonly used by medicinal chemists," said Fionn O'Hara, PhD, a postdoctoral researcher in the Baran laboratory and a co-author of the recent study (1). In many cases, these reagents can be used to sequentially make more than one modification to a starting compound. The groups that can be attached with the new reagents include trifluoromethyl, difluoromethyl, trifluoroethyl, monofluoromethyl, isopropyl and triethylene glycol monomethyl ether.

To show the ability of the reagents to work in biological media, Baran's team used the reagents to difluoromethylate or trifluoromethylate heterocycles in a solution of cell lysate as well as to serve as a buffer medium (i.e., tris), which is commonly used in laboratory-dish tests.

Baran's laboratory collaborated with scientists from Pfizer. "They provided insight into the types of compounds that would be valuable, assistance with optimization, and, most importantly, testing of the chemistry in their drug-discovery laboratories, where it is meant to be used," Baran said.

The first of the zinc sulfinate salts, DFMS, also known as Baran difluoromethylation reagent, is being manufactured in bulk and marketed by chemical suppliers, according to the TSRI release. Baran is working to expand his initial toolkit to provide more heterocycle-modifying choices.

Click chemistry

Other researchers at TSRI recently reported on reaction-tracking techniques used to elucidate the mechanism behind the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction. This reaction involves the use of copper compounds to catalyze the linkage of two functional groups, a nitrogen-containing azide and a hydrocarbon alkyne, to make a stable five-membered heterocycle, 1,2,3-triazole. The CuAAC process is an example of click chemis-

Small-molecule drug development: recent study suggests limited binding sites

A new study of both computer-created and natural proteins suggests that the number of unique pockets, sites where small-molecule pharmaceutical compounds can bind to proteins, is small, thereby, offering an explanation of the difficulty in mitigating side effects in drug design.

Studying a set of artificial proteins and comparing them to natural proteins, researchers at the Georgia Institute of Technology (Georgia Tech) concluded that there may be no more than about 500 unique protein pocket configurations that serve as binding sites for small-molecule ligands, according to a May 20, 2013 university press release. "Our study provides a rationalization for why a lot of drugs have significant side effects because that is intrinsic to the process," said Jeffrey Skolnick, a professor in the School of Biology at Georgia Tech and co-author of the recent study (1). "There are only a relatively small number of different ligand-binding pockets. The likelihood of having geometry in an amino-acid composition that will bind the same ligand turns out to be much higher than anyone would have anticipated. This means that the idea that a small molecule could have just one protein target can't be supported."

Binding pockets on proteins are formed by the underlying secondary structure of the amino acids, which is directed by hydrogen bonding in the chemistry, which allows formation of similar pockets on many different proteins even those that are not directly related to one another. "You could have the same or very similar pockets on the same protein, the same pockets on similar proteins, and the same pockets on completely dissimilar proteins that have no evolutionary relationship," said Skolnick in the release. "In proteins that are related evolutionarily or that have similar structures, you could have very dissimilar pockets. This helps explain why we see unintended effects of drug and opens up a new paradigm for how one has to think about discovering drugs."

The implications for medicinal chemistry could be significant. To counter the impact of unintended effects, drug developers will need to know more about the available pockets to avoid affecting binding locations that are also located on proteins crucial to life processes. If the unintended binding takes place on less crucial proteins, the side effects may be less severe. In addition, drug development could also move to a higher level by examining the switches that modulate the activity of proteins beyond binding sites. "The strategy for minimizing side effects and maximizing positive effects may have to operate at a higher level," Skolnick said. "You are never going to be able to design unintended binding effects away. But you can minimize the undesirable effects to some extent."

In their study, the researchers used computer simulations to produce a series of artificial proteins that were folded, but not optimized for function. Using an algorithm that compared pairs of pockets and assessed the statistical significance of their structural overlap, they analyzed the similarity between the binding pockets in the artificial proteins and the pockets on a series of native protein, according to the release. The artificial pockets all had corresponding pockets on the natural proteins, suggesting that the simple physics of folding has been a major factor in development of the pockets. "This is the first time that it has been shown that side effects of drugs are an inherent, fundamental property of proteins rather than a property that can be controlled for in the design," Skolnick added. "The physics involved is more important than had been generally appreciated."

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try, a term coined in 2001 by Nobel Laureate K. Barry Sharpless to describe a set of bond-forming reactions useful for the rapid assembly of molecules with desired function (3). Click transformations are easy to perform, give rise to their intended products in high yields with little or no byproducts, and work well under many conditions (3). Organic azides, as highly energetic and selective functional groups, were used in organic dipolar cycloadditions with olefins and alkynes among the reactions fulfilling the click criteria, but the low reaction rate of the azide–alkyne cycloaddition did not make them useful in the click context until the copper-catalyzed reaction (3). The copper-catalyzed reaction was reported separately by Sharpless et al. in the United States and Melda et al. in Denmark (3). It transforms organic azides and terminal alkynes into the corresponding 1,4-disubstituted 1,2,3-triazoles, in contrast to the uncatalyzed reaction, which requires higher temperatures and provides mixtures of 1,4- and 1,5-triazole regioisomers (3).

The simplicity and reliable performance of CuAAC under diverse conditions, including in water and in the presence of oxygen, has made it a useful method whenever covalent stitching of small molecules or large biopolymers is needed, exemplified by protein and nucleic-acid labeling, *in vitro* and *in vivo* imaging, and drug synthesis, according to an Apr. 4, 2013 TSRI press release.

"Despite its many uses, the nature of the copper-containing reactive intermediates that are involved in the catalysis had not been well understood, in large part due to the promiscuous nature of copper, which rapidly engages in dynamic interactions with other molecules," said Valery Fokin, an associate professor at TSRI, who was principal investigator for the new study examining the reaction-tracking techniques of CuAAC, in the TSRI April 2013 release.

The researchers explained that despite the widespread use of copper-catalyzed cycloaddition reactions, the mechanism of these processes was difficult to establish due to multiple equilibria between several reactive intermediates (4). They reported that real-time monitoring of a representative cycloaddition process by means of heat-flow reaction calorimetry showed that monomeric copper acetylide complexes are not reactive toward organic azides unless an exogenous copper catalyst was added. Additional experiments with an isotopically enriched exogenous copper source showed the stepwise nature of the carbon–nitrogen bond-forming sequence and the equivalence of the two copper atoms within the cycloaddition steps (4).

The research revealed that in the CuAAC reaction, two copper-containing catalytic units—copper centers—are needed to help build the new triazole structure. "By monitoring the reaction in real time, we showed that both copper atoms are needed and established the involvement of copper-containing intermediates that could not be isolated or directly observed," said Brady Worrell, a co-author in the study in the TSRI April 2013 release. The researchers used isotopic copper as one of the copper centers to track the reaction. "We hypothesized that the two copper centers would have distinct roles, but found unexpectedly that their functions during key steps in the reaction are effectively interchangeable," said Jamil Malik, also a co-author, in the TSRI 2013 release.

The research not only provides insight into the CuAAC reaction, but also enables development of new reactions that exploit weak interactions of copper catalysts with carbon–carbon triple bonds. Fokin and his team have begun to devise new reactions in which one copper center can be replaced with a different element, to pursue complementary biocompatible and efficient techniques, notes TSRI.

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Microwave spectroscopy for enantiomeric detection of chiral molecules

Chirality plays an important role in pharmaceutical compounds, and methods for detecting and quantifying chirality remains challenging. Researchers at Harvard University and the Center for Free-Electron Laser Science (CFEL) and the Max Planck Institute in Germany recently reported on the use of enantiomer-specific detection of chiral molecules by microwave spectroscopy.

The researchers pointed out that the spectroscopic methods of circular dichroism and vibrational circular dichroism are commonly used in analyzing chiral molecules. These methods, however, have limitations in electric dipole approximation as the resultant weak effects produce weak signals and require high sample densities (1). In contrast, nonlinear techniques probing electric-dipole-allowed effects have been used for sensitive chiral analyses of liquid samples. Influenced by these methods, the researchers carried out nonlinear resonant phase-sensitive microwave spectroscopy of gas-phase samples in the presence of an adiabatically switched nonresonant orthogonal electric field. They used this technique to map the enantiomer-dependent sign of an electric dipole Rabi frequency onto the phase of emitted microwave radiation (1). They describe theoretically how this results in a sensitive and species-selective method for determining the chirality of cold gas-phase molecules. They implemented the approach experimentally to distinguish between the *S* and *R* enantiomers of 1,2-propanediol and their racemic mixture. They reported that this technique produced a large and definitive signature of chirality and has the potential to determine the chirality of multiple species in a mixture.

"We can soon measure mixtures of different compounds and determine the enantiomer ratios of each," said Melanie Schnell, co-author of the study in a CFEL release. In a next step, the researchers plan to apply the technique in a broadband spectrometer at CFEL that could then measure the enantiomer ratios in mixtures of substances. In the longer run, the method opens the door to develop a technique for separating enantiomers.

Reference

1. D. Patterson, Melanie Schnell, and John M. Doyle, *Nature*, 497 (7450), 475-477, 2013.

New Strategies for Evaluating Biopharmaceutical Stability

ON-DEMAND WEBCAST

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EVENT OVERVIEW:

Unlike traditional small-molecule drugs, stability studies for biopharmaceuticals can be one of the most critical and challenging aspects of large-molecule drug development. The size and complexity of most proteins provide fertile ground for intramolecular changes and multiple routes of degradation, and to assess their effects, each must be correlated to the bioactivity of the drug. With the average cost to develop a biopharmaceutical well over $1 billion, and shelf life being an important driver of success, understanding these effects prior to long-term stability profiling is critical to sound decision-making and efficient development strategy. This 60-minute webcast will provide insight from leading industry experts on the common pitfalls of biopharmaceutical stability testing, regulatory agencies' expectations for supporting data, and the latest analytical techniques that can improve information and streamline the development process.

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- Identifying the battery of stability-indicating methods needed for stability testing
- Learning ways to extend the shelf life of your product through correlation of stability data

PRESENTERS:

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Senior Scientific Advisor
ABC Laboratories

Wayland Rushing, Ph.D.
Senior Scientific Advisor
ABC Laboratories

Carrie L. Anderson
Senior Scientist, Vaccine Analytical Development
Merck & Co.

John Geigert, PhD., RAC
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Patricia Van Arnum
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Pharmaceutical Technology

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

Methods for Identifying Out-of-Trend Results in Ongoing Stability Data

Adrijana Torbovska and Suzana Trajkovic-Jolevska

It is important to distinguish between out-of-specification (OOS) and out-of-trend (OOT) results in stability studies. The authors discuss three methods for identification of OOT results—the regression-control-chart method, the by-time-point method, and the slope-control-chart method—and further compare the z-score method and the tolerance interval in OOT analysis. The results highlight the need for issuing a regulatory confirmed guideline for identification of OOT results for ongoing stability data.

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Submitted Nov. 9. 2012; Accepted Dec. 5, 2012.

The two terms out-of-trend (OOT) and out-of-specification (OOS) results are in many cases confused by pharmaceutical companies and regulatory agencies. OOT results are defined as a stability result that does not follow the expected trend, either in comparison with other stability batches or with respect to previous results collected during a stability study (1). OOT results are not necessarily OOS, but they do not look like a typical data point. Although OOT results are a serious problem, the scientific literature and regulatory guidelines do not fully address this issue.

According to FDA's *Guidance for Industry: Investigating Out-Of-Specification (OOS) Test Results for Pharmaceutical Production* (2), OOT results should be limited and scientifically justified. The guideline, however, does not define the process for identification of OOT results in stability data. The CMC Statistics and Stability Expert Teams of the Pharmaceutical Research and Manufacturers of America made an attempt to address this problem by suggesting several statistical methods for the identification of OOT results (3). The proposed statistical methods were redesigned and analyzed for the purposes of this study.

The aim of this study was to make a statistical confirmation of the statistical methods, which will prove their functionality in identification of OOT results in ongoing stability data within a batch or data among batches. In addition, a comparison was made between the z-score method and the tolerance interval (TI) in terms of defining the limits for identification of the present OOT result.

Materials and methods

For the purpose of this study, data from ongoing stability studies of a final drug product with a shelf life of 36 months were used. The ongoing studies were conducted on 10 batches of Product X. Product X is manufactured in a tablet dosage form and consisted of one active substance with defined strength of 10 mg and packaged in a primary aluminium–polyvinyl chloride (Al–PVC) blister and a secondary package. The ongoing studies were conducted for 36 months in stability chambers at a constant temperature of 25 °C ± 2 °C and relative humidity of 60% ± 5% in accordance with the ICH guideline Q1A(R2) (4).

The reported data are single data results for the assay attribute, calculated as a percentage of the declared active substance concentration. The assay attribute was analyzed

Figure 1: Least-square line method for the time period of 0–9 months.

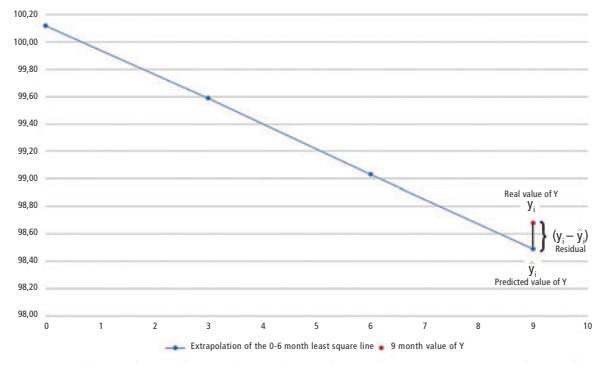

Figure 2: Representation of the historical data with the use of the by-time-point method.

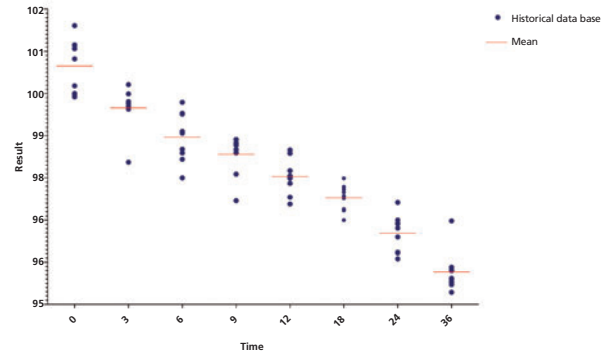

Table I: Regression-control chart for the tenth batch.

Months	Y	Expected Y	Residuals	z
0	100.12	100.13	-0.0050	-0.577
3	99.59	99.58	0.0100	1.155
6	99.03	99.04	-0.0050	-0.577
9	98.68	98.49	0.1900	21.939
12	98.34	98.14	0.2050	1.653
18	95.82	97.36	-1.5440	-14.962
24	94.70	95.04	-0.3363	-0.216
36	95.41	92.04	3.3682	5.834

Table II: The regression-control chart method limits from the tolerance interval (TI) and z-values for the corresponding TI values.

Time period (months)	TI -	z for TI -	TI +	z for TI +
0–6	-0.137	-15.819	0.137	15.819
0–9	-0.882	-9.757	0.978	9.768
0-12	-0.763	-7.762	0.921	7.762
0–18	-4.344	-6.201	4.726	7.343
0–24	-3.559	-5.453	3.983	6.835

in accordance to the validated internal method of the manufacturer at the time points of 0, 3, 6, 9, 12, 18, 24, and 36 months in all of the tested batches.

The first nine batches were used as historical data for the purposes of the by-time-point method and the slope-control-chart-method in addition to which the tenth batch was compared and analyzed. The historical data were used to define the limits for identification of present OOT results in the tenth batch; the regression-control-chart-method analysis was conducted only on the tenth batch.

In addition, simulated data also were implemented. The simulated data were comprised of eight test time points for each of the 10 simulated batches. Unlike the experiment, in the simulation, the 10 batches were tested using the regression-control-chart method. In the by-time-point method and the slope-control-chart method, however, the historical data of the real batches were used to individually analyze the 10 randomly generated batches.

Regression-control-chart-method. The regression-control-chart method is used to compare the results within the batch and detect present OOT results. For the purpose of this method, the tenth batch was examined. Several least-square regression lines were fit to the suitable data (5). The first regression line was constructed from the three results for assay at the first three time points (0, 3, and 6 months). With extrapolation of that regression line, the expected values for Y and the Y residuals were calculated (see **Figure 1**) (6). The procedure was then repeated by gradually adding all the other consecutive time points.

The next step was to calculate the mean and standard deviation (σ) of the Y residuals of the regression line. As a result, a sum of five means and standard deviations corresponding to the time periods (0–6, 0–9, 0–12, 0–18, and 0–24 months) were constructed. To identify the present OOT result, the z-score test was used to calculate the z-value for each Y residual at each time point. The z-value is based on the means and standard deviations of the defined time periods (see **Table I**). The z-value was limited to $-3 < z < +3$, where 99.73% of the future results are expected to enter the interval within these limits.

Testing the precision of the TI in comparison to the z-score test, the TI for the same five time periods was calculated according to the suitable equation with defined certainty (α=0.027) and confidence (γ=0.95) (7). To compare the two methods for each TI value, a corresponding z-value was calculated (see **Table II**).

By-time-point method. The by-time-point method is used to determine whether a result is within expectations on the

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Table III: Mean value and standard deviation of the historical data and z-value for Batch 10.

Months	Mean value	Standard deviation	z-value for Batch 10
0	100.65	0.6358	-0.835
3	99.66	0.5152	-0.134
6	98.97	0.5866	0.108
9	98.56	0.4846	0.243
12	98.03	0.4197	0.741
18	97.53	0.3126	-5.464
24	96.69	0.4406	-4.517
36	95.77	0.4888	-0.746

Table IV: The by-time-point method limits from the tolerance interval (TI) and z-values for the corresponding TI values.

TI -	z for TI-	TI +	z for TI+
97.21	-5.41	104.09	5.41
96.87	-5.41	102.45	5.42
95.80	-5.40	102.14	5.41
95.94	-5.41	101.18	5.40
95.76	-5.41	100.30	5.41
95.84	-5.40	99.22	5.41
94.31	-5.40	99.07	5.40
93.13	-5.41	98.41	5.39

basis of experiences from other batches measured at the same stability time point. To minimize the α and β error (6), batches that comprise the historical data (Batches 1 to 9) were individually tested for present OOT results. In addition, calculations for the mean and standard deviation of the values for the tested attribute were made from the historical data for each time point individually (see **Figure 2**).

To identify the present OOT result, the z-score test was used to calculate the z-value for each value of Y (the assay result) of the tenth batch. Analysis was made at each time point using the mean and the standard deviation from the historical data corresponding to the tested time point (see **Table III**). The value of z was again limited to $-3 < z < +3$.

The TI was also calculated with α=0.027 and γ=0.95 for each time point. To compare the two methods for each TI value, a corresponding z-value was calculated (see **Table IV**).

Slope-control-chart method. The slope-control-chart method is commonly used when it is necessary to compare the results between several tested batches or between the currently tested batch and other batches from the historical database. For the purpose of this experiment, control limits were defined from the historical data and then used to test Batch 10 for the presence of OOT results. For each time point, a least-squares regression line that includes all data up to that time point was constructed. The regression line was constructed from the data of 0, 3, and 6 months, and the slope of that line was calculated. The procedure was repeated until the last tested time point of the ongoing stability study. The mean and standard deviation of the slopes for the given time intervals were calculated. The slope-control chart was then constructed (see **Table V**).

To identify the present OOT result, the z-score test was used to calculate the z value for the slope at each time period of Batch 10. The value of z was limited to $-2 < z < +2$, provided that 95.45% of the future values will enter the interval of these limits. Unlike the previous two methods for identification of OOT results, where the absolute value of the result was analyzed, in this method, the authors analyzed the values for the slope. Because small changes in the slope value cause a significant change in the regression line (and in this case it would mean the kinetics of degradation), for this model, narrower limits for the z-value were chosen.

Additionally, the TI also was calculated from the slope values at each time interval. In this case, however, the TI was calculated with defined α=0.045 and γ=0.95, for proper comparison with the limits determined by the z-score test (7). In order to compare the two methods for each TI value, a corresponding z-value was calculated (see **Table VI**).

Results and discussion

The simulation gave the same results as the experiment. Therefore, this study was focused only on elaborating the experiment on its own. It must be noted that the obtained limits in this experiment will only apply to this final product in the given dosage form, strength, and primary and secondary packaging.

With the use of the regression-control-chart method, three OOT results were detected in the time points of 9, 18, and 36 months (see **Table I**). The result in the 9-month time point deviates approximately 0.19%. The result in the 18-month time point deviated by 2%, and the result in the 36-month time point deviated by 3% from the expected value according to the regression line. Taking into consideration that in the time point of 9 months, the regression line was constructed of only three points; the result was falsely identified as an OOT result, and it was not investigated further. In terms of the control limits, the z-score test provides a constant limit of 3σ standard deviations throughout the whole regression line unlike the TI that limits the results within 15σ for the time point of 6 months to 5σ for the time interval of 24 months.

The by-time-point method identified two OOT results in the time points of 18 and 24 months (see **Table III**). Compared with the results from the historical data for the appropriate time points, the results of the tested batch

Table V: Slope-control chart and the z-values for Batch 10.

Time period (months)	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9	Batch 10	z
0–6	-0.327	-0.290	-0.348	-0.215	-0.082	-0.330	-0.503	-0.207	-0.225	**-0.182**	**0.840**
0–9	-0.239	-0.179	-0.272	-0.222	-0.127	-0.264	-0.339	-0.219	-0.228	**-0.163**	**1.166**
0–12	-0.233	-0.143	-0.243	-0.190	-0.171	-0.204	-0.278	-0.214	-0.227	**-0.149**	**1.542**
0–18	-0.175	-0.132	-0.203	-0.159	-0.144	-0.146	-0.201	-0.167	-0.193	**-0.223**	**-2.056**
0–24	-0.140	-0.152	-0.169	-0.155	-0.144	-0.129	-0.163	-0.160	-0.167	**-0.233**	**-5.977**
0–36	-0.102	-0.133	-0.136	-0.137	-0.135	-0.103	-0.142	-0.126	-0.138	**-0.158**	**-1.995**

deviated approximately by 2%. According to the z-value the results deviated 5σ from the average value of the historical data at those time points. In this method, the z-score test provided limits of 3σ, and the TI constant limit of 5.4σ (see **Table IV**).

The slope-control-chart method analysis resulted in identifying two OOT results (see **Table V**). The present OOT result for the time point of 18 months deviated 2.05σ and for 24 months deviated 5.97σ from the average value for the slope, according to the z-value. The TI, on the other hand, provided limits of 3.6σ, which were wider than the limits comprised from the z-score test. Ultimately, each manufacturer is responsible for choosing its own control limits, suitable to the analysis of the corresponding final product with its own strength and primary and secondary packaging.

This study provided a thorough explanation of the proposed methods for identification of OOT results. The methods were redesigned and improved to achieve proper evaluation of the tested stability data. The experiment revealed the positive and negative features of the proposed methods, thereby defining their appropriate use.

The regression-control-chart method allowed analysis of the results within a batch, which was achieved by comparing the absolute values of the results and the predicted values that were obtained by extrapolation of the regression line. The main disadvantage of this method was the necessity of having results for each time point due to the fact that the construction of the regression line was based on gradually adding the values in each subsequent time point. For the time period of 0–9 months, the regression line was constructed only from three points; therefore, the calculations for the predicted values were prone to an error. This method, however, is suitable for identification of present OOT results in cases where there is no historical stability data.

The by-time-point method provides analysis of the results in each time point individually, and no assumptions about the shape of the degradation curve are needed. The main advantage of the method was that the absence of having a result in any time point did not affect the analysis of the previous or next time point result. In conclusion, this method is more appropriate for analysis of the results of the first four time points. The main disadvantage is that a large history of data is preferred for proper use of this method. This method, therefore, is not suitable for analysis of ongoing stability data at the beginning of the production of the final product.

Table VI: The slope-control chart method limits from tolerance intervals (TI) and z values for the corresponding TI values.

Time period (months)	TI -	z for TI -	TI +	z for TI +
0–6	-0.706	-3.606	-0.144	3.605
0–9	-0.447	-3.617	-0.017	3.616
0–12	-0.357	-3.600	-0.065	3.618
0–18	-0.263	-3.609	-0.075	3.606
0–24	-0.201	-3.569	-0.011	3.569
0–36	-0.182	-3.579	-0.074	3.574

By measuring the slope of the regression line, the slope-control-chart method provided analysis of each time point individually by analyzing the influence of each time-point result on the regression line. Any small change in the value of the tested attribute from point to point was precisely recorded in the slope value of each time point. It is advised, therefore, to establish slightly narrower limits in this method in comparison to the first two methods. The main disadvantage of this method is that if the test of the attribute were omitted in any time point for various reasons, the limits of that time point may not be appropriate.

In terms of the limits, the z-score method produced limits that remain constant around all of the time points in all of the methods for OOT results identification. The dependence of the TI on the number of samples included

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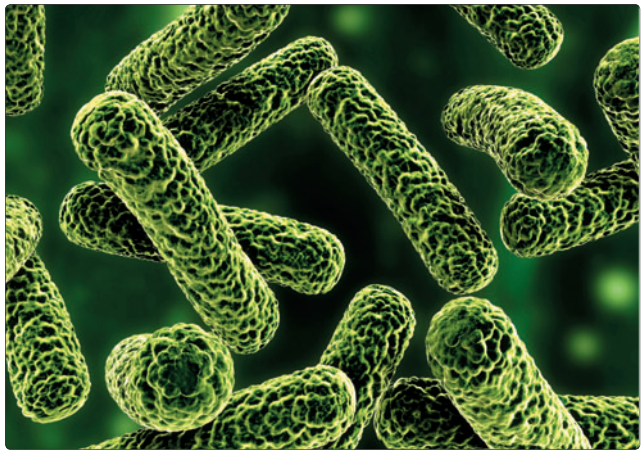
Understanding Biological Indicator Grow-Out Times—Part II

John R. Gillis, Gregg A. Mosley, John B. Kowalski, Garrett Krushefski, Paul T. Nirgenau, Kurt J. McCauley, and Philip M. Schneider



Biological indicators (BIs) are used to monitor the efficacy of sterilization processes for medical products. BIs contain high numbers of bacterial spores (generally 10^4 to 10^6) that are highly resistant to the sterilization process for which they are designed. This paper is Part II of a series reporting on the range and distribution of grow-out times for BIs exposed to sublethal sterilization processes. The authors describe studies to confirm and extend their original findings that the grow-out times for a set of nonsterile BIs approximates a normal distribution and that one or more BIs from such a set would occasionally exhibit delayed outgrowth.

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Submitted: July 11, 2012. Accepted: July 18, 2012.

This paper is Part II of a series reporting on the range and distribution of grow-out times for biological indicators (BIs) exposed to sublethal sterilization processes. Part I described grow-out times for self-contained BIs with *Geobacillus stearothermophilus* spores on paper carriers that were exposed to moist-heat sterilization processes at 121 °C (1). The studies described in this paper were performed to confirm and extend the authors' original findings that the grow-out times for a set of nonsterile BIs approximates a normal distribution, and occasionally, one or more BIs from such a set would exhibit a delayed outgrowth. Delayed nonsterile BIs were almost exclusively found in sets of BIs where the average number of surviving colony-forming units (CFU) was estimated at less than 1.0/BI unit.

The previous studies exposed BIs to moist-heat sterilization processes that gave results that met the FDA protocol for establishing a reduced incubation time (RIT) (2). Sets of exposed BIs that have 30 to 80 nonsterile out of the 100 tested have a range estimate of 0 to 5 CFU per BI (1). In the studies reported in this article, the FDA RIT protocol was again followed, but testing was also performed using exposures based on the calculated survival time that is referenced in the *US Pharmacopeia* (USP) and Association for the Advancement of Medical Instrumentation (AAMI)/International Organization for Standardization (ISO) documents (3–5). The calculated survival exposure time results in BIs with approximately 100 surviving CFU, a much higher average value when compared to the results found after exposure of BIs to the conditions required to meet the FDA RIT protocol.

For the studies reported in this article, the moist-heat sterilization processes tested were expanded to include exposures at 132 °C, 134 °C, and 135 °C. BIs exposed to hydrogen peroxide (H_2O_2) vapor were self-contained with 10^6 spores of *G. stearothermophilus* inoculated on stainless-steel discs. BIs exposed to ethylene oxide (EO) gas and chlorine dioxide (ClO_2) gas sterilization processes were also tested. For the EO and ClO_2 processes, BIs with *Bacillus atrophaeus* spores were used; both paper spore strips and self-contained BIs with paper carriers were tested.

Materials and methods

BIs. A list of the BIs used in the studies is shown in **Table I**, which lists the spore species, spore crops, sterilization process, BI configuration, spore carrier, spore population,

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Table I: Biological indicator (BI) test sample matrix.

Spore species	Sterilization process	BI configuration	Spore carrier	Spore population	BI lots	Media lots	Spore crops
Geobacillus stearothermophilus	Moist heat	Self-contained	Paper	10^5	14	14	5
	Hydrogen peroxide vapor	Self-contained	Stainless steel	10^6	6	6	3
Bacillus atrophaeus	Ethylene oxide gas	Self-contained	Paper	10^6	6	6	6
	Chlorine dioxide gas	Spore strip culturing set with tubed media	Paper	10^6	3	3	3

Table II: Time-to-nonsterile results for *Geobacillus stearothermophilus* biological indicators (BIs) exposed to moist heat.

	Unexposed controls	Calculated survival time exposure 121 °C	FDA reduced incubation time (RIT) protocol exposure		
			132 °C	134 °C	135 °C
Lots tested	10	5	3	3	3
Number of nonsterile BIs per set	980	500	36, 67, 60 (165/300)	39, 68, 63 (170/300)	35, 40, 48 (123/300)
Average time to (in hours):					
1st positive	2.27	2.98	3.42	3.27	3.38
50% nonsterile BIs	3.27	3.90	4.54	4.79	4.86
95% nonsterile BIs	3.90	4.90	7.0	8.0	7.9
Last nonsterile BIs	4.55	5.43	9.0	9.38	9.07
Delayed growth BIs	0	0	1 between 8.27 h and 120 h	1 between 9.38 h and 168 h	0
Incubation time (in hours) between 1st nonsterile and 95% nonsterile BIs	1.63	1.92	3.58	4.73	4.52

and BI lots used. Seventeen different spore crops were used that were produced over a period of five years; samples were tested from 29 commercial batches of BIs. The BIs tested had spores inoculated onto paper or stainless-steel carriers. Spores inoculated onto glass fiber discs were not tested. Specific types and lots of microbiological media were used for grow-out time testing to minimize variability associated with the recovery media aspect of the testing. Each BI lot was produced with a separate media lot; therefore, 29 different media lots were included in the testing.

Incubation of BIs. Unexposed controls and exposed BIs were incubated for seven days and the time to exhibit a nonsterile result was recorded. *G. stearothermophilus* BIs were incubated at 60 ± 2 °C in a Smart-Well incubator system (Mesa Laboratories). Grow-out of a BI was detected by measuring color change in the growth medium and was recorded in 0.01-hour increments. The test BIs were removed from the Smart-Well incubator after 24 hours and placed in a conventional incubator at 60 ± 2 °C for the remainder of the seven days. *Bacillus atrophaeus* BIs were incubated in a conventional incubator at 37 ± 2 °C and were monitored for nonsterility by visual inspection at intervals between 30 and 60 minutes when nonsterile BIs were frequently occurring. Intervals were extended to several hours when there were less frequent changes in numbers of nonsterile BIs. When it appeared that the majority of the nonsterile BIs were detected, observation intervals were significantly decreased for the remainder of the seven days. The delayed nonsterile BI would be detected, but the precise time delay would not be known.

Delayed nonsterile definition. A BI was classified as a delayed nonsterile unit if the timing of the observed growth was 150% or greater than the incubation time needed for 95% of the other BIs in the test set to indicate the nonsterile response.

Equipment. Moist-heat, H_2O_2 vapor, and EO gas sterilization processes were performed in resistometers that met the requirements of ISO 18472: 2006 (6). All ClO_2 exposures were performed in a custom resistometer manufactured by

Table III: Time-to-nonsterile results for *Geobacillus stearothermophilus* biological indicators (BIs) exposed to hydrogen peroxide vapor.

	Unexposed controls	Calculated survival time exposure	FDA reduced incubation time (RIT) protocol exposure
Lots tested	3	3	3
Number of nonsterile BIs per set	300	297	40, 45, 75 (160/300)
Average time to (in hours):			
1st positive	2.98	3.54	4.70
50% nonsterile BIs	3.84	4.61	5.78
95% nonsterile BIs	5.3	6.0	9.9
Last nonsterile BIs (excluding delayed growth BIs)	5.70	8.57	14.75*
Delayed growth BIs	0	1 at 12.68 h	3 (total) 1 at 18.47 h 2 at 18.23 h and 18.25 h
Incubation time (in hours) between 1st nonsterile and 95% nonsterile BIs	2.32	2.46	5.2

*14.75 h is the average time for the last nonsterile BI. The 15.07 h was a data point that was three hours later than the next nearest data point and was therefore, labeled delayed.

ClorDiSys. There are no published guidelines describing a resistometer for chlorine dioxide gas exposures.

Exposure conditions. *Unexposed controls:* Unexposed BIs were used as a control. Sets of 100 BIs for each for the various BI configurations were incubated to provide a baseline response for each spore type, carrier, media, and incubation condition.

Calculated survival time exposure: The calculated survival time was based on the resistance of the specific spores/carrier combination to a particular sterilization mode (3–5). This exposure was designed to reduce the number of viable spores by three to four orders of magnitude, which resulted in each BI having approximately 100 surviving spores. The formula for calculation of the survival time exposure is:

Survival time exposure = D-value x (log10 of the population – 2)

Because the calculated survival time exposure was intended to yield a spore concentration of approximately 100 spores per BI, all BIs were expected to be nonsterile. If all BIs were not nonsterile, then one had to review the two input values required for this calculation—the D-value and the population count. The D-value is a more complicated value to measure accurately and if the D-value is overstated, the calculated survival time exposure would be longer in duration and thus might result in some/all of the BIs testing as sterile. For a surviving population of approximately 100 spores/BI, all exposed BIs should be nonsterile 100% of the time.

FDA RIT protocol exposure: The FDA RIT protocol exposure requires a sublethal process that, on groups of 100 BIs, yields at least 30 and no more than 80 positive BIs. The most probable number of spores per BI when 30 out of 100 BIs tested are nonsterile is 0.357. The most probable number of spores per BI when 80 out of 100 BIs tested are nonsterile is 1.609. This results in a practical range of 0–5 surviving CFU/BI. Additionally, some BIs in every set of 100 would not have any surviving spores (6).

Results and discussion

Moist-heat exposures. All moist-heat exposures were performed with self-contained BIs with 10^5 spores of *G. stearothermophilus* inoculated onto paper carriers (see **Table I**).

Unexposed controls: Nine lots of 100 and one lot of 80 BIs were incubated at 60 ± 2 °C to determine a baseline for time to nonsterile results (see **Table II**). The first nonsterile BI was detected at 2.27 hours. Ninety-five percent of all BIs exhibited nonsterile results by 3.9 hours. The incubation duration between the first nonsterile BI and 95% BIs nonsterile was 1.63 hours. There was a slight tail in the curve due to a small number of BIs exhibiting somewhat longer grow-out times. It was concluded that this distribution of grow-out times was due to natural variation often seen in biological systems.

Calculated survival time exposures at 121 °C: Five lots of 100 BIs were exposed to the calculated survival time process and incubated as previously described (see **Table II**). The average time for the first nonsterile BI for the five lots tested was 2.98 hours. Ninety-five percent of all BIs exposed to these conditions were nonsterile in 4.9 hours. The 4.9 hours of incubation required to observe 95% of the BIs as nonsterile was 20% longer than that found with the unexposed controls. No delayed nonsterile BI's were observed in this series of exposures.

Table IV: Time-to-growth positive results for *Bacillus atrophaeus* biological indicators (BIs) exposed to ethylene oxide gas.

	Unexposed controls	Calculated survival time exposure	FDA reduced incubation time (RIT) protocol exposure
Lots tested	3	3	6
Number of nonsterile BIs per set	300	300	44, 38, 70, 30, 57, 70 (309/600)
Average time to (in hours):			
1st positive	7.5	18.2	21.96
50% nonsterile BIs	9.83	20.8	35.86
95% nonsterile BIs	10.2	21.3	62.9
Last nonsterile BIs (excluding delayed growth BIs)	10.2	22.5	63.5
Delayed growth BIs	0	0	3 (total) 3 between 72 h and 168 h
Incubation time (in hours) between 1st nonsterile and 95% nonsterile BIs	2.7	3.1	40.9

FDA RIT protocol exposures: Three lots of 100 of BIs were exposed to a moist-heat sterilization process that resulted in 30 to 80 nonsterile BIs for each of the lots (see **Table II**).

The average time for the three lots exposed at 132 °C for the first nonsterile BI was 3.42 hours. Ninety-five percent of the BIs exposed to 132 °C were nonsterile at 7.0 hours. The incubation duration from first nonsterile BI to 95% nonsterile was 3.58 hours, which was nearly twice as long as that observed for the calculated survival time exposure.

At 134 °C, the average time for the three lots tested for the first nonsterile BI was 3.27 hours, which was slightly less than that observed at 132 °C. Ninety-five percent of the BIs exposed to 134 °C were nonsterile in 8.0 hours, which was one hour longer than at 132 °C. The incubation duration from the first nonsterile BI to 95% nonsterile was 4.73 hours, which was about one hour longer than that observed for the exposures at 132 °C.

At 135 °C, the average time in the three lots for the first nonsterile BI was 3.38 hours. Ninety-five percent of the BIs exposed to 135 °C were nonsterile at 7.9 hours. The incubation duration from the first nonsterile BI to 95% nonsterile was 4.73 hours, which was also approximately one hour longer than that observed for the exposures at 132 °C.

There were two delayed nonsterile BIs observed, one exposed at 132 °C and one exposed at 134 °C. The BI exposed to 132 °C grew out between 8.27 hours and 120 hours of incubation. The BI exposed to 134 °C grew out between 9.38 hours and 168 hours of incubation. The actual grow-out times for these two BIs is believed to be less than 120 and 168 hours, but these BIs were not monitored after 10 hours so the exact grow-out time was not determined.

Using the probability table shown in Part I of this study, the authors projected that 61% of the 335 nonsterile BIs exposed at 132 °C and 134 °C were likely to contain only one surviving spore (1). The two delayed grow-out results accounted for only 0.6% of the nonsterile BIs.

The grow-out time results for the moist-heat exposures at 121 °C, 132 °C, 134 °C, and 135 °C are presented in vertical scatter plots (see **Figure 1, Panel A**). The vertical scatter plots illustrate the variability in grow-out time for the different exposure temperatures and different lots of BIs. The difference in grow-out time results between the survival time and RIT exposures is clearly illustrated.

The 121 °C calculated survival time exposure results were much more consistent from first to last nonsterile BI grow out. There were a few BIs that were slower to grow out, but the delay was not significant. Lots 1, 2, 3, and 4 had one to three BIs that were noticeably slower in grow out; the delay average was approximately 0.5 hours.

All of the RIT exposure results were much more variable than the results for the calculated survival exposures. The grow-out time results for the moist-heat exposures are graphically illustrated in **Figure 2, Panel A**.

Hydrogen peroxide vapor exposures. All H_2O_2 exposures were performed with self-contained BIs with 10^6 spores of *G. stearothermophilus* inoculated onto stainless steel discs (see **Table I**).

Unexposed controls: Three lots of 100 BIs were incubated at 60 ± 2 °C to determine a baseline for the time required for BIs to exhibit nonsterile results (see **Table III**). The average time for the first nonsterile BI in the three lots was 2.98 hours. Ninety-five percent of all BIs tested exhibited nonsterile results by 5.3 hours. The incubation duration between the first nonsterile BI and 95% BIs nonsterile was 2.3 hours.

Calculated survival time exposures: Three lots of 100 BIs were exposed to the calculated survival time and incubated as previously described (see **Table III**). The average time for the first nonsterile BI in the three lots was 3.54 hours. Ninety-five percent of the BIs were nonsterile in 6.0 hours. This incubation duration from the first nonsterile BI to 95% nonsterile BIs was 2.46 hours. This result was very

Table V : Time-to-nonsterile results for *Bacillus atrophaeus* biological indicators (BIs) exposed to chlorine dioxide gas.

	Unexposed controls	Calculated survival time exposure	FDA reduced incubation time (RIT) protocol exposure
Lots tested	3	2	4
Number of nonsterile BIs per set	300	200	69, 73, 75, 41 (258/400)
Average time to (in hours):			
1st positive	5.5	12.75	15.0
50% nonsterile BIs	6.0	14.25	17.0
95% nonsterile BIs	6.1	15.5	32.25
Last nonsterile BIs (excluding delayed growth BIs)	6.4	21.5	46
Delayed growth BIs	0	0	5 (total) 1 between 38.50 h and 138 h 2 between 46 h and 138 h 2 between 38 h and 41 h
Incubation time (in hours) between 1st nonsterile and 95% nonsterile BIs	0.6	2.75	17.5

similar to that observed with the unexposed controls. Two of the three lots tested did not yield 100 nonsterile BIs; one lot had 99 nonsterile BIs and the second lot had 98 nonsterile BIs. It is believed that the calculated survival time exposure was inappropriately long due to inaccuracy of the D-value determination. If the D-value is overstated, the average number of surviving spores would be less than approximately 100 resulting in some of the BIs being sterilized in the survival time exposure.

One delayed nonsterile BI was observed in one of the lots tested. For this BI, the grow-out time was 4.11 hours longer than that of the adjacent nonsterile test result. This delayed nonsterile BI took 223% longer to exhibit nonsterility than 95% of the nonsterile BIs. This was the only delayed nonsterile BI observed for the calculated survival time exposures for any of the processes examined in this study.

FDA RIT protocol exposures: Three lots of 100 BIs were exposed to H_2O_2 vapor that resulted in 30 to 80 BIs nonsterile per lot (see **Table III**). The average time for the first nonsterile BI for the three lots was 4.7 hours. Ninety-five percent of the BIs were nonsterile by 9.9 hours of incubation. The duration of incubation from the first nonsterile BI to 95% nonsterile was 5.2 hours, which was nearly twice as long as that for the BIs exposed to the calculated survival time exposure.

There were also three delayed nonsterile BIs observed; one BI from one lot and two BIs from another lot. The delayed grow-out time was approximately 5.5 hours longer than that of the adjacent nonsterile test results. This incubation duration was 190% of the time to 95% of the nonsterile BIs.

It appeared that significant nonlethal spore damage occurred at this exposure condition, which was designed to yield a surviving population of 0 to 5 CFU (7–9). Using the probability table in Part I of this study, the authors projected that 66% of the 160 nonsterile BIs would contain only one surviving CFU (1). However, only 2.5% of the nonsterile BIs had a delayed response.

All grow-out time results for all H_2O_2 exposures are presented in vertical scatter plots in **Figure 1, Panel B**. They are also presented graphically in **Figure 2, Panel B**.

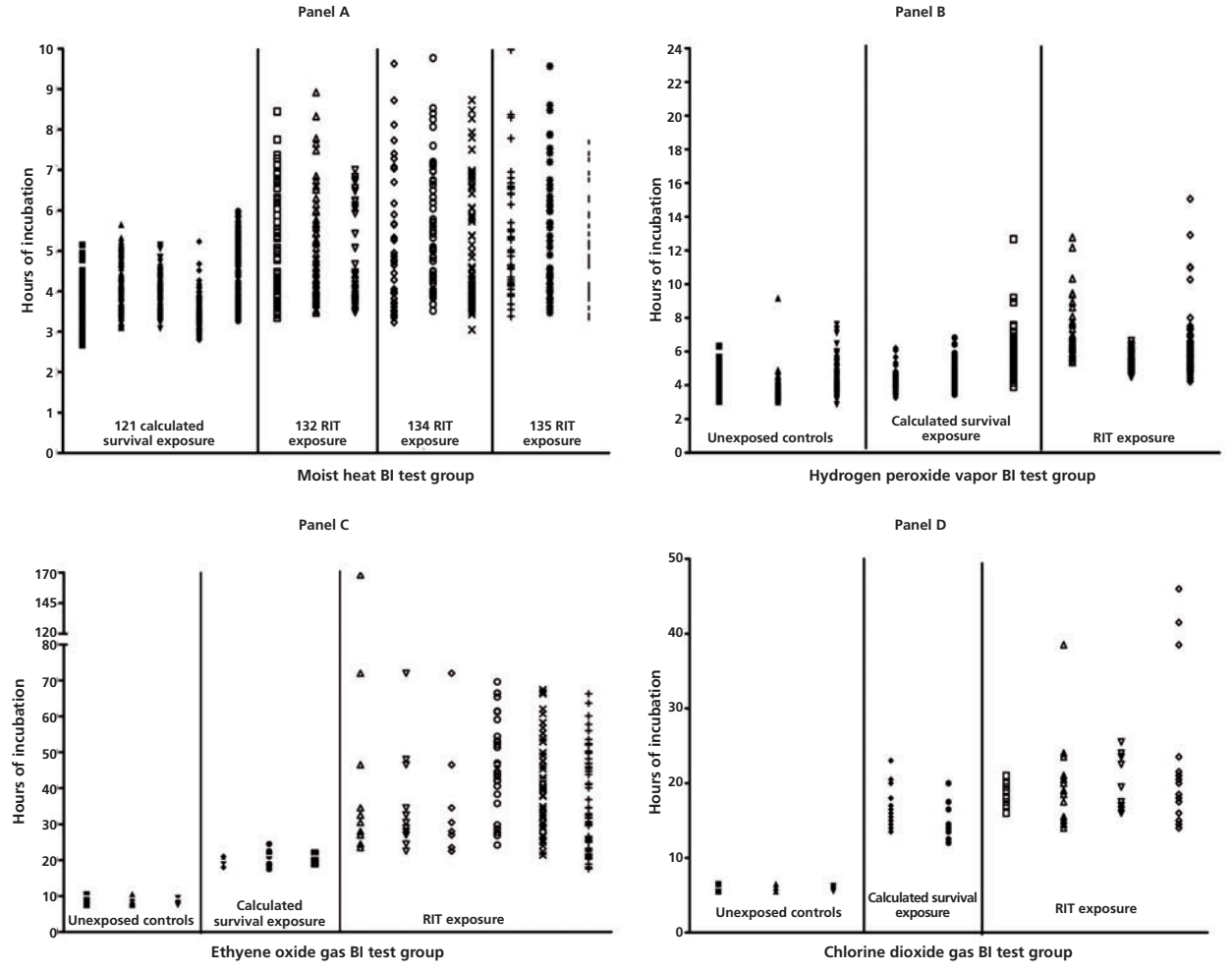
Ethylene oxide gas exposures. All EO exposures were performed with self-contained BIs with 10^6 spores of *B. atrophaeus* inoculated onto paper carriers (see **Table I**).

Unexposed controls: Three lots of EO BIs were incubated at 37 ± 2 °C in a conventional incubator to determine a baseline value for the time required for BIs to exhibit nonsterile results (see **Table IV**). The average time for the first nonsterile BI in the three lots was 7.5 hours. Ninety-five percent of all BIs were nonsterile in 10.2 hours. The incubation time between the first nonsterile BI and 95% nonsterile BIs was 2.7 hours; no delayed nonsterile BIs were observed.

Calculated survival time exposures: The calculated survival time exposures were performed using three lots of 100 BIs. The average time for the first nonsterile BI in the three lots was 18.2 hours. Ninety-five percent of all BIs exposed to these conditions were nonsterile in 21.3 hours. The duration of incubation between the first nonsterile BI and 95 % nonsterile was 3.1 hours. This duration was approximately 15% longer than that found with the unexposed controls. No delayed nonsterile BIs were observed.

FDA RIT protocol exposures: Six lots of BIs were exposed to yield 30 to 80 BIs nonsterile per lot (see **Table IV**). The average time for the first nonsterile BI for the six lots tested was 21.96 hours. Ninety-five percent of all BIs exposed to these

Figure 1: Vertical scatter plots of grow-out time results for exposure to moist heat (Panel A), hydrogen peroxide vapor (Panel B), ethylene oxide gas (Panel C), and chlorine dioxide gas (Panel D). RIT = reduced incubation time.



conditions were nonsterile in 62.9 hours. The duration of incubation from the first nonsterile BI to 95% nonsterile was 40.94 hours, which was approximately 13 times longer than that found with the calculated survival time exposures.

Delayed nonsterile BIs were observed with two of the lots. Two BIs were observed in one lot and one BI was observed in the second lot. The delayed nonsterile BIs grew out between 72 hours and 168 hours of incubation. Using the probability table in Part I of this study, the authors projected that 66% of the nonsterile BIs would contain only one surviving CFU (1). However, only 0.97% of the nonsterile BIs exhibited a delayed grow-out time.

The grow-out time results for all BIs exposed to EO gas are illustrated in the vertical scatter plots in **Figure 1, Panel C**. A graphical expression of these data appears in **Figure 2, Panel C**.

Chlorine dioxide gas exposures. All ClO_2 exposures were performed with paper spore strips and tubed media culture sets. The paper strips contained 10^6 *B. atrophaeus* spores and were packaged in Tyvek Mylar envelopes (see **Table I**).

Unexposed controls: The unexposed controls consisted of three lots of spore strip culture set BIs which were incubated in a conventional incubator at 37 ± 2 °C. The average time for the first nonsterile BI for the three lots was 5.5 hours. Ninety-five percent of all BIs were nonsterile in 6.1 hours. The incubation duration between the first nonsterile BI and 95% nonsterile was 0.6 hours. No delayed nonsterile BI's were observed in this series of tests.

The grow-out time for the ClO_2 unexposed controls was faster than the time required for the EO gas unexposed controls. The spores, carrier, and incubation conditions were the same. The recovery media used to culture the spore strip had a different formulation for the ClO_2 BIs, which resulted in the faster grow-out time.

A vertical scatter plot for each of the exposures is shown in **Figure 1, Panel D**. A graphical representation of these data is illustrated in **Figure 2, Panel D**.

Calculated survival time exposures: Two lots of ClO_2 spore strip culture sets were used for these exposures. The average time for the first nonsterile BI for the two

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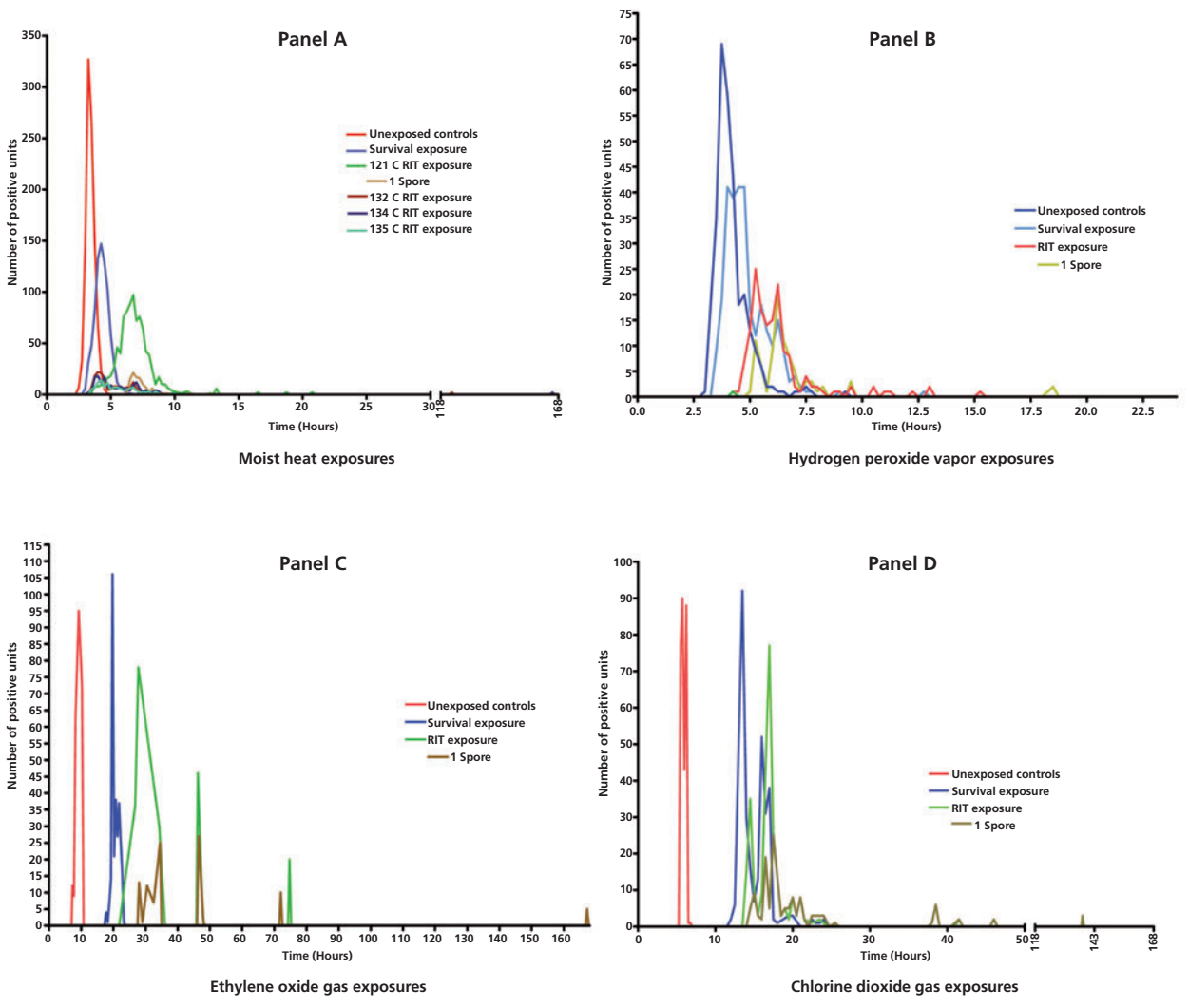
Figure 2: Graphical illustration of grow-out time results for exposure to moist heat (Panel A), hydrogen peroxide vapor (Panel B), ethylene oxide gas (Panel C), and chlorine dioxide gas (Panel D). RIT = reduced in incubation time.



lots tested was 12.75 hours. Ninety-five percent of all BIs exposed to these conditions were nonsterile in 15.5 hours. The incubation duration from the first nonsterile BI to 95% nonsterile was 2.75 hours, which was 4.5 times longer than that observed with the unexposed controls. No delayed nonsterile BIs were observed.

FDA RIT protocol exposures: The RIT exposures were performed using four lots of spore strip culture set BIs. The average time for the first nonsterile BI for the three lots tested was 15 hours. Ninety-five percent of all BIs exposed to these conditions were observed nonsterile in 32.25 hours. The incubation duration from the first nonsterile BI to the 95% nonsterile was 17.25 hours, which was 6.27 times longer than that observed with the calculated survival time.

Three delayed nonsterile BIs were observed. Two BIs exhibited a delayed response in one lot and one BI in each of the other lots tested. Using the probability table in Part I of this study, the authors projected that 53% of the nonsterile BIs would contain only one surviving CFU (1). However, only 1.2% of the nonsterile BIs exhibited a delayed response. One lot of BIs was tested twice in this series, thus there are four sets of results but only three separate lots of BIs.

The grow-out time results for all BIs exposed to ClO_2 gas is illustrated using vertical scatter plots in **Figure 1, Panel D**. A graphical representation of these data sets is shown in **Figure 2, Panel D**.

Conclusions

The study showed several key findings as outlined below:

- Grow-out time results, regardless of the mode of sterilization, approximates a normal distribution for all exposure conditions.
- This study indicates that the dynamics of spore germination and out-growth are very similar regardless of the sterilization mode to which the BIs are exposed. This study included moist heat at 121 °C, 132 °C, 134 °C, and

135 °C as well as H_2O_2 vapor, EO gas, and ClO_2 gas. It is unlikely that different bacterial endospores would respond differently to other sterilizing agents.

- The data continue to support the conclusion that there is an inverse relationship between the number of surviving spores on a BI and the overall range of grow-out time. The time required to obtain an acceptable cell density and/or cumulative metabolic activity requires less time when the starting level of viable spores is higher than when it is lower.
- Grow-out times were shorter for *G. stearothermophilus* spores than for *B. atrophaeus* spores.
- The timing of the calculated survival time exposures yielded nonsterile results faster and more consistently than the FDA RIT protocol exposures. No delayed nonsterile results were observed in the calculated survival time exposures that provided results with all BIs nonsterile.
- Delayed nonsterile BIs were observed with all sterilization modes tested. All delayed nonsterile BIs were observed when the exposures yielded dichotomous results (some BI replicates nonsterile and some BI replicates sterile).
- Delayed nonsterile BIs almost certainly contained a single viable spore. If two or more spores are present on the BI and only one exhibited delayed germination and/or outgrowth, the other spore would mask this condition and yield a nonsterile result in a time similar to a BI with a single spore that was not severely damaged.
- Delayed nonsterile results were found in a very small portion of the BIs exposed. The total number of BIs exposed that yielded a dichotomous result was approximately 2400. The number of BIs that were nonsterile was 1188. The total number of delayed nonsterile BIs observed was 13 or 1.1% of all nonsterile BIs. Delayed nonsterile results for each sterilization mode evaluated were as follows:
  - —Moist heat: 0.44% delayed nonsterile BIs
  - —H_2O_2: 2.5% delayed nonsterile BIs
  - —EO: 0.97% delayed nonsterile BIs
  - —ClO_2: 1.2 % delayed nonsterile BIs.

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Peer Reviewed—Stability Testing—*contin. from page 51*

in the calculation was a major drawback for its use in the methods for OOT results identification. The TI requires a large number of results, which is difficult to meet in everyday practice within the pharmaceutical industry. The freedom of choosing the z-score limits remains a decision of each manufacturer, and it is determined according to its own requirements.

Conclusion

The pharmaceutical industry still lacks having a proper guideline for the identification of present OOT results among ongoing stability data. As a result, many pharmaceutical companies are not harmonized in the way they conduct this type of analysis.

In this study, three methods for identification of OOT results in ongoing stability data were proposed: the regression-control-chart method, the by-time-point method, and the slope-control-chart method. To obtain more accurate identification of existing OOT results, simultaneous use of all three methods is advised, which will result in getting a visual image of the results of the analyzed batches. The use of the z-score method for defining the limits for the OOT results is preferred. Lastly, the study highlighted the necessity of issuing a regulatory confirmed guideline for identification of OOT results within ongoing stability data.

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Industry Perspectives: Achieving Solutions for the Challenge of Poorly Water-Soluble Drugs

Adeline Siew, PhD and Patricia Van Arnum

A multifaceted approach is needed to resolve the myriad of challenges in developing oral formulations of poorly soluble drugs.

Bringing a drug candidate to successful commercialization is always a challenging task, but it is one that has been made more difficult through the increase of poorly water-soluble drugs. It is estimated that 40% of new drug compounds may be regarded as poorly soluble with that percentage even higher for certain therapeutic classes (1). Improving the oral absorption and bioavailability of poorly soluble drugs is crucial for pharmaceutical companies seeking to bring efficacious drugs to patients in dosing regimens and product forms that are easy to use, affordable, and facilitate patient compliance.

To understand the extent of this challenge and the technologies for bioavailability/solubility enhancement, *Pharmaceutical Technology* partnered with the Catalent Applied Drug Delivery Institute (see sidebar, "Advancing drug delivery") in the second annual *Catalent–Pharmaceutical Technology Landscape Drug Delivery Survey*. The study surveyed formulation scientists involved with oral product development in pharmaceutical companies in the United States, Canada, and Europe to understand their key concerns and the technologies used to resolve problems of solubility and bioavailability. The results showed that there are a myriad of technical concerns attendant to solubility/bioavailability and many factors have to be taken into consideration in deciding which approach is optimal for a given API.

Adding complexity to formulations

Consistent with the 2012 survey (2), solubility/bioavailability enhancement remains a major issue. Ninety-two per-

Advancing drug delivery

Building cross-functional and scientific expertise is crucial for successful drug development. To that end, Catalent launched the Catalent Applied Drug Delivery Institute in 2012 as a way to promote innovation, knowledge-sharing, and collaboration between industry leaders, academic experts, customers, and regulators as a means to enhance understanding of available, emerging, and future drug-delivery technologies.

In early 2013, Terry Robinson was appointed executive director of the Catalent Applied Drug Delivery Institute. She joined the executive leadership team, which also includes other Catalent executives: Kurt Nielsen, PhD, chief technology officer and senior vice-president of R&D; Cornell Stamoran, vice-president, corporate development and strategy; Julien Meissonnier, PhD, platform director, R&D; Elliott Berger, global vice-president, marketing and strategy; and Akan Oton, director of technology licensing and product ventures.

The Catalent Applied Drug Delivery Institute further includes pharmaceutical industry executive and inventor, Ralph Lipp, PhD, as the founding advisory board member. The institute will leverage his help and the expertise of more than 100 Catalent scientists and collaborations with external subject-matter experts in the US and Europe. Some of these experts include Abu Serajuddin, PhD, professor at St. John's University and Rajesh Dave, PhD, professor at the New Jersey Institute of Technology. The institute's partnerships help to promote the development of innovative technologies in various areas, such as taste-masking, bioavailability enhancement, particle engineering, hot-melt extrusion, oral vaccines, and oral macromolecules.

To cultivate that knowledge sharing, the Institute plans to hold educational events. The first educational training event, "Overcoming Bioavailability Challenges," will be held June 12 in Somerset, New Jersey. The event will feature industry and academic experts discussing: innovative bioavailability strategies for overcoming challenges in the delivery of poorly soluble drugs; key benefits of using new drug-delivery technology platforms; and insights on industry and academia collaborations to help deliver better treatments for patients. To learn more about the Catalent Applied Drug Delivery Institute, visit: http://www.drugdeliveryinstitute.com.

IMAGE COURTESY OF CATALENT PHARMA SOLUTIONS

cent of the 2013 survey respondents have worked with Biopharmaceutics Classification System (BCS) Class II (low solubility, high permeability) or Class IV (low solubility, low permeability) compounds, and half always or often work with these compounds.

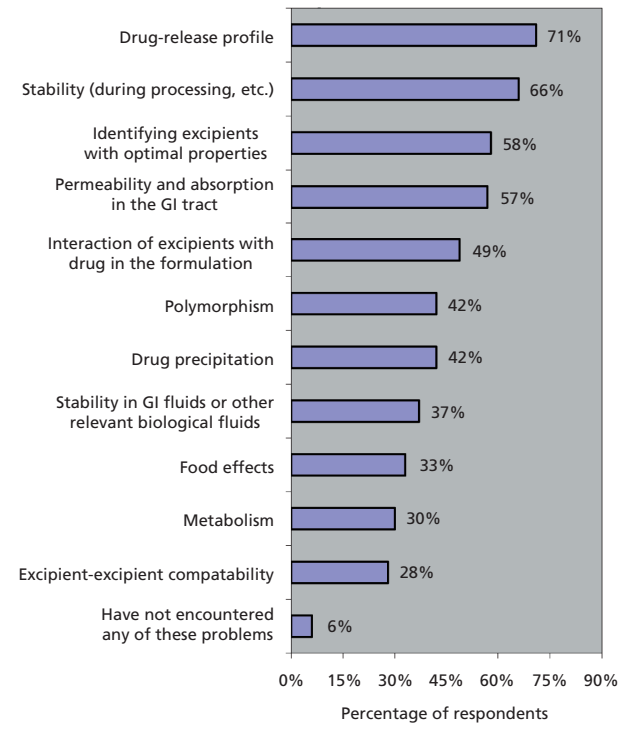
A poorly soluble compound adds to the complexity of formulation development. "Countless poorly soluble compounds never reach human clinical studies," comments Kurt Nielsen, PhD, chief technology officer and senior vice-president of R&D at Catalent Pharma Solutions. "Better understanding the chemistry of the drug, solubilizers (e.g., polymers, surfactants, and lipids) and the various salt/crystal forms can get more drug candidates through preclinical testing."

The survey results confirm these observations. The two top problems identified by respondents when working with poorly soluble drugs were optimizing the drug-release profile (71% of respondents cited) and stability (66% cited) (see **Figure 1**). More than half (58%) cited difficulties in identifying excipients with optimal properties, and 49% identified excipient–API interactions as a concern. As would be expected, permeability and absorption in the gastrointestinal tract were also key issues.

Figure 2 provides more in-depth insight. Fifty-three percent of respondents said that stability of the API was either "always" or "often" a challenge, and 46% cited inter- and intra-patient variability. Other formulation challenges, such as dose uniformity and the food effect on absorption, also were commonly encountered problems (see **Figure 2**). "Often times, the bioavailability of a poorly soluble drug increases when given with high-fat meals," explains Catalent's Nielsen. "The changes in bioavailability induced by food can negatively impact assessment of safety and efficacy. In addition, eliminating the food effect simplifies dosing instructions for patients," he adds.

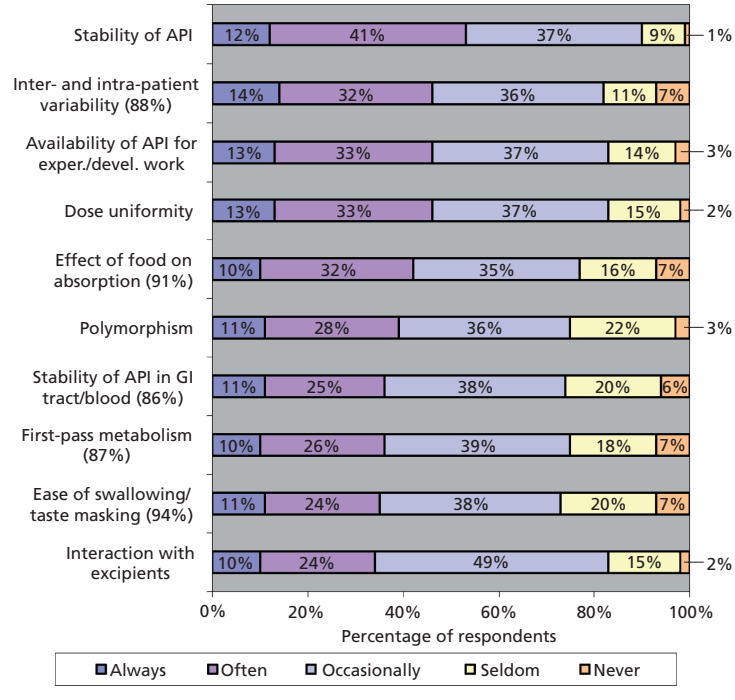
Other concerns, such as swallowing/taste masking, were cited as frequent problems by 35% of respondents. "Child- and senior-friendly products rely on taste masking for dosing convenience," says Nielsen. "Poorly soluble drugs often need multiple technolo-

Figure 1: Problems encountered when developing oral formulations of poorly soluble APIs.



GI is gastrointestinal

Figure 2: Frequency of challenges when developing a formulation for a poorly soluble API.



* For the categories of inter- and intra patient variability, 88% of respondents answered, for effect of food on absorption (91% answered), first-pass metabolism (87% of respondents answered), and ease of swallowing/taste-masking (94%) answered). In all other categories, 100% of respondents answered

GI is gastrointestinal

gies in the same engineered particle to achieve the required taste profile."

Evaluating the technologies

Given the complexity of formulation challenges when working with poorly soluble drugs, the survey examined the importance of factors in deciding on a solubilization strategy. The physiochemical properties of the API and safety were both major factors (see **Figure 3**). Interestingly, the depth and availability of expertise, including third-party expertise, were significant factors. Ninety-three percent of respondents said that internal expertise and knowledge were "very important" or "somewhat important," and access to third-party expertise and knowledge were commensurately important (see **Figure 3**). More than half (53%) said bioavailability and solubility issues were a reason to partner.

Seeking solutions

The survey also asked respondents to evaluate solubilization/bioavailability enhancement strategies (see **Figure 4**). "Enhancing bioavailability is multifactorial and involves approaches to optimize the API, the formulation, and the processing technology to develop the final product form," explains Nielsen. "These factors are codependent and synergistic in most cases, so a 'best-in-class' toolkit for solubility enhancement includes multiple technologies," he adds. For example, a solubilization approach may first address salt formation and excipient selection. Other technologies, such as particle milling/micronization, nanoparticles, spray-drying, hot-melt extrusion, liquid-filled capsules, and softgels, can be further evaluated for suitability for a given formulation challenge.

Editorial podcast: strategies for bioavailability enhancement

Kurt Nielsen, PhD, chief technology officer and senior vice-president of R&D at Catalent Pharma Solutions, discusses solubilization strategies with *Pharmaceutical Technology* Executive Editor Patricia Van Arnum. Listen to the podcast at www.PharmTech.com/CatalentSolubility.

contin. on page 66

Figure 3: Importance of factors in choosing a solubilization strategy.

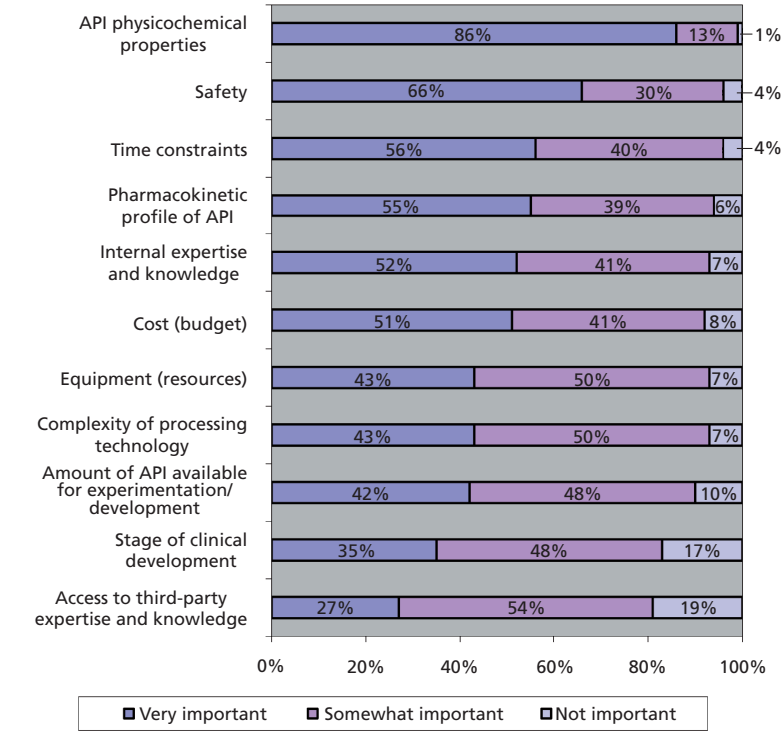
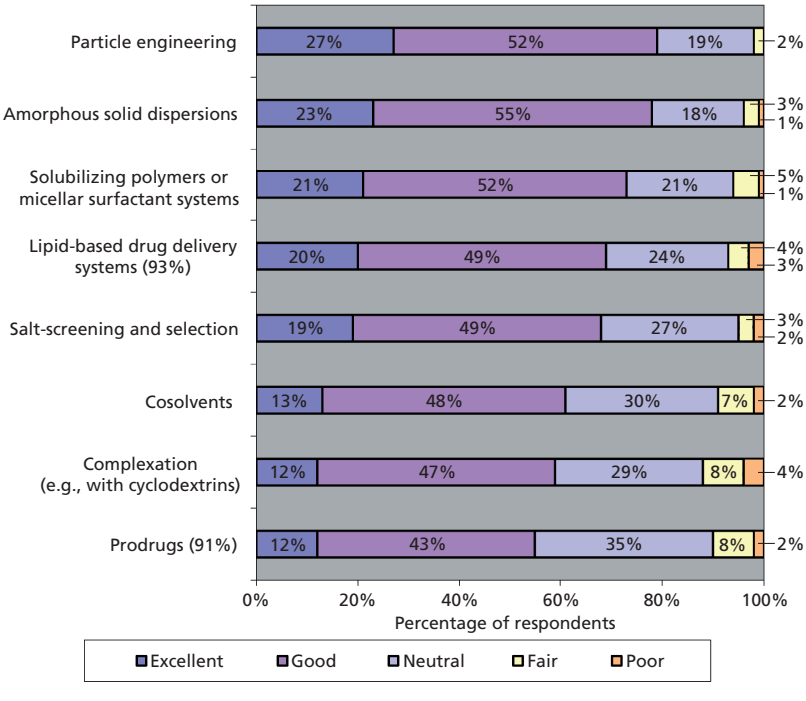


Figure 4: Evaluation of strategies/technologies in addressing poor solubility.



* Lipid-based drug delivery systems, 93% of respondents answered; prodrug, 91% of respondents answered. All other categories, 100% of respondents answered.

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- Learn how to design controlled-release formulations solutions that remain robust in the presence of alcohol and of the critical material, formulation and performance attributes of alcohol-resistant coatings

Presenters

Dr. Rina Chokshi
Project Leader for Controlled Release Technology
FMC Biopolymer

Om Anand
FDA

Peter Timmons, PhD
Executive Director, Drug Product Science and Technology, Research And Development
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Drug Approval Trends Don't Extend to CMOs

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Jim Miller

Approvals of new drugs are on an upward swing, but only a few CMOs are benefiting.

New drug approvals by FDA continued their upward advance in 2012, but CMOs didn't benefit much from the improvement. The data suggest that the market share of dose CMOs may have peaked.

In 2012, FDA's Center for Drug Evaluation and Research (CDER), which approves new small-molecule and biologic therapeutic drugs, approved 101 new drug applications (NDAs). This level was on par with the 102 new drugs approved in 2011 and continues the recovery in NDA approvals that started in 2008 (see **Figure 1**).

The composition of the new approvals was particularly noteworthy. Of the 101 NDA approvals, 39 were for new molecular entities (NMEs) (i.e., drugs containing an API that was approved for the first time). The NMEs included 10 biologics and 28 small molecule drugs. This level was the most NME approvals in more than seven years.

There were 62 non-NME drugs approved (i.e., drugs containing a previously approved API). Of those, 47 were approved via the 505(b)(2) route, which provides for a simplified approval process for new formulations of previously approved drugs. The 505(b)(2) process is particularly popular with specialty pharmaceutical and generics-drug companies because it is a lower-cost and lower-risk process for developing new drugs than developing NMEs.

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Outsourcing trends remain unchanged

While the approvals trend grew stronger, the propensity for outsourcing the manufacturing of these new drugs remained flat. Overall, dose manufacturing was outsourced for 42% of the NDAs approved in 2012, which was consistent with the 41% average for the previous six-year period (see **Figure 2**). Both NMEs and non-NMEs were outsourced at the 42% rate.

The propensity to outsource was largely a function of the nature of the approval and the size of the company getting the approval. Global and mid-size biopharma companies were more likely to outsource their non-NMEs than their NMEs; the global biopharma companies did not outsource dose manufacturing for any of their biologics approvals, but did outsource some of their small-molecule approvals. Small companies outsourced dose manufacture for most of their new approvals, both NME and non-NME, including 100% of their biologic approvals. As one would expect, generic-drug companies outsourced few of their new approvals.

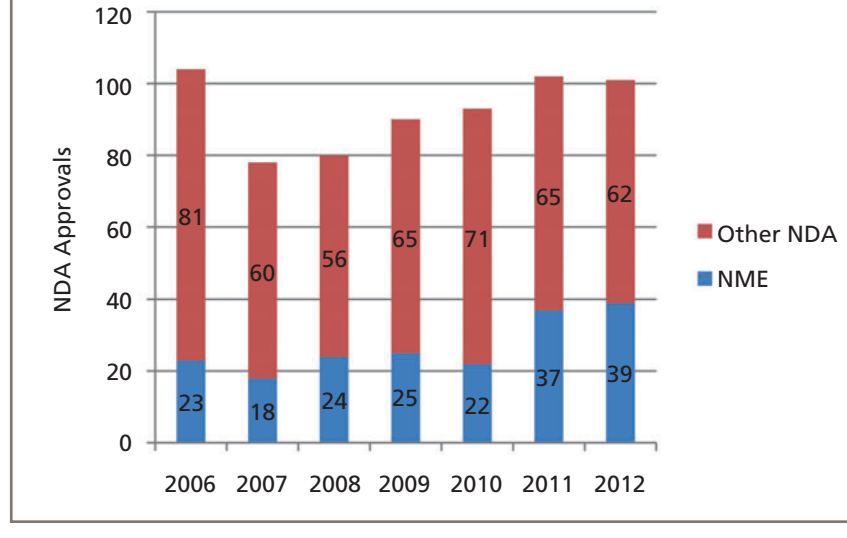
A total of 28 different dose CMOs benefited from new product approvals in 2012. Only six had more than one approval, with Catalent (six new approvals) and Patheon (four new approvals) leading the way.

PharmSource analysis of eight years of FDA approvals data suggests that the acceptance of the CMO business model and its penetration of the biopharmaceutical industry have remained relatively unchanged throughout most of the past decade. NME dose-form outsourcing has remained relatively constant for the past seven years as the industry is governed by two basic truths: smaller companies have a strong tendency to outsource while global biopharma companies have a strong preference to keep products in-house.

Outsourcing strategies

Among global bio/pharma companies, attitudes and strategies regarding contract manufacturing appear to be well entrenched. Out of the 22 global bio-

Figure 1: New drug application (NDA) approvals, 2006-2012. NME is new molecular entity.



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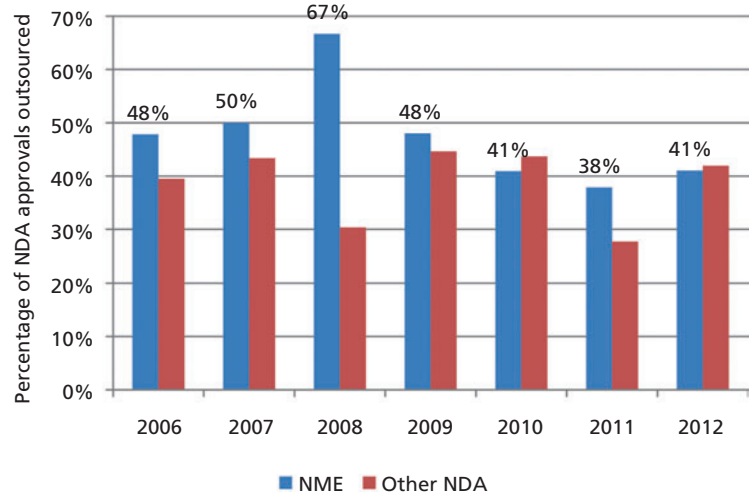
pharma companies, nine companies—including Abbott/Abbvie, Astellas, Bayer, and Novo Nordisk—outsourced none of their new NDA approvals during the 2005–2012 period. On the positive side, four companies have outsourced 50% or more of their NDA approvals received during the past eight years, and another four have outsourced 30% or more of their approvals. Unfortunately, six of the eight companies have averaged less than one approval per year over the period.

The data on outsourcing of recent NDA approvals must be analyzed carefully because the majority of the contracts for these products were signed three-to-five years ago (i.e., in 2007–2009). Given the long cycles between contract signings and product approvals, strategy changes triggered by the 2008-2009 financial crisis and the patent cliff probably are not yet reflected in the manufacturing arrangements of recently approved products.

Nevertheless, it does appear that outsourcing's share of dose manufacturing is stuck in the 40–45% range, and further penetration may be difficult to achieve. Global biopharmaceutical companies have been shrinking their manufacturing networks and shrinking their product pipelines, but they are investing in captive biologics manufacturing capacity and building new manufacturing facilities to serve the growing emerging markets.

Figure 2: Share of new drug application (NDA) approvals outsourced, 2006-2012. NME is new molecular entity.



Among smaller companies, those companies that develop new biologics may be unable to afford their own sterile manufacturing facilities, but small companies developing solid-dose products face a much lower capital expenditure for owning captive capacity.

CMO executives like to proclaim that outsourcing is growing, and so long as the number of new product approvals continues to rise, they will be right. But just as a rising tide lifts all boats, a receding tide can leave many of them beached. The large number of CMOs receiving approvals again highlights the highly fragmented nature of the sector; so many CMOs have received just a few or no approvals that one wonders how they can stay in business.

The battle for market share among CMOs is getting intense, and we sense that customers are able to drive more favorable terms, including lower prices and other concessions. A number of major CMOs have accepted this reality by turning their efforts increasingly to proprietary products. We continue to believe that the CMO industry is headed for a period of consolidation. **PT**

Drug Delivery – *contin. from page 62*

Ralph Lipp, PhD, head of Lipp Life Sciences, member of the advisory board of the Catalent Applied Drug Delivery Institute, and formerly vice-president of pharmaceutical sciences R&D at Eli Lilly, offered several examples of commercial drugs to illustrate the diversity of solubility/bioavailability enhancement strategies (3). The HIV treatment Kaletra (ritonavir and lopinavir) uses solid dispersions produced by hot-melt extrusion, and the antifungal drug Sporanox (itraconazole) is produced as a solid dispersion by spray-drying. The antinausea drug Emend (aprepitant) uses particle engineering (i.e., nanocrystals/media milling) to improve bioavailability. And the protease inhibitor Fortovase (saquinavir) is formulated in a self-emulsifying drug-delivery system in a softgel capsule (3).

Looking ahead

These advances in solubility and bioavailability enhancement are an integral part of meeting the needs of patients for efficacious drugs. "Several essential medicines based on advanced oral drug-delivery technologies provide significant value to patients around the globe today already," says Lipp. "In light of the current trend toward low solubility and poor bioavailability drug candidates in the pipelines of innovators, this class of technologies is of increasing relevance. Formulation scientists applying proven and novel oral drug-delivery technologies will significantly contribute to enabling the next generation of important medicines," concludes Lipp.

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AbbVie and Alvine Will Collaborate on Celiac Disease Therapy

AbbVie and Alvine Pharmaceuticals, a developer of celiac disease therapeutics, announced that they have agreed to develop an oral treatment, currently in Phase II development, for patients with celiac disease.

ALV003 is an investigational oral therapy composed of two recombinant, gluten specific enzymes (a cysteine protease [EP-B2] and a prolyl endopeptidase [PEP]), that degrade gluten *in vitro* and in human clinical testing. The therapy may reduce the symptoms and intestinal injury associated with celiac disease in patients attempting to adhere to a gluten-free diet.

Halo Pharma, Altus Formulation Announce Collaboration

Halo Pharma has taken a minority ownership position in, and established a formal collaboration with, the drug formulation and development company Altus Formulation. Altus uses proprietary technologies and approaches to solve pharmaceutical formulation and delivery problems.

The collaboration enables Halo the capabilities to offer an entire suite of proprietary scientific and technical solutions designed to solve intractable issues in such areas as drug solubility, bioavailability, tamper and abuse deterrence, and precisely managed drug-dosage delivery. The aforementioned solutions include a range of non-sterile and sterile dosage forms.

"We are delighted to have this new association with Altus," said Halo Pharma CEO Clive Bennett. "[The collaboration] will allow Halo to provide novel proprietary solutions to clients with difficult formulation problems in addition to those already available public domain and client originated solutions that we have historically offered."

Kemwell Expands Analytical Services Capabilities in India

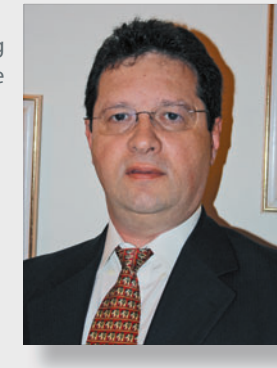
The biopharmaceutical CDMO Kemwell Biopharma has expanded its analytical capabilities in India to service a full-time equivalent contract for a multinational pharmaceutical company.

"This project and lab expansion further reflects Kemwell's commitment to its customers," said Ninad Deshpanday, president of R&D at Kemwell. "Kemwell has invested in a dedicated facility to meet the needs of this very important customer. The scope of the project includes method transfer, stability sample analyses, and analytical method validation for various projects for the customer. We are actively looking to invest in and grow our development business."

Kemwell's R&D division currently employs more than 100 scientists and provides services ranging from formulation development, analytical development, and validation to clinical-trial manufacturing. The new analytical lab is equipped with 10 HPLCs, one UPLC, and nine dissolution apparatus and other major analytical instruments. Kemwell will employ 15 scientists dedicated for the aforementioned project.

Q&A with

Roberto Darienzo, *Chief Operating Officer, Halo Pharmaceutical*



PharmTech:
What strategies are you planning to employ to remain competitive in the contract pharmaceutical development and commercial manufacturing industry?

Darienzo:
Clients expect us to be flexible, fast, and obviously to have competitive costs. We will achieve that by implementing best practices in operational excellence initiatives so that we have highly performing equipment, greatly trained and motivated teams, and that we are creative enough to find solutions to the most diverse problems our clients may face with their products. We believe we can generate ideas for development solutions, bringing those solutions to them better than our competition.

PharmTech:
Do you see a new industry trend emerging?

Darienzo:
There are several companies working not only in the discovery of new molecules, but also in taking known molecules or products and developing new ways of formulating them, new ways to release or deliver them to patients, reducing their abuse potential, improving their safety, efficacy, absorption, reducing side effects or effective dosage, etc. Obviously reducing the abuse potential of narcotic analgesic formulations (as well as other frequently abused drugs) is an active area at the moment, and an area in which Halo is currently working on numerous controlled substances.

PharmTech:
How is your company responding to regulators' intensifying emphasis on inspections and product quality?

Darienzo:
We are obliged to be absolutely perfect in our quality and compliance. So far, as a CDMO that started in 2008 that has had annual general and preapproval inspections because of our sterile area and the introduction of new products, we have yet to receive a 483 observation. This is very difficult, and never to be taken for granted, but it's a record we are determined to continue. Because of the number of clients we are now dealing with, we have an average of one audit per week, and have a tremendous source of GMP consulting advice. This gives us the opportunity to learn fast, to be fully updated on trends and new concepts, and to improve continuously every week.

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MANUFACTURING EQUIPMENT & SUPPLIES

Tablet-coating adhesion fixture

Brookfield Engineering's CT3 Texture Analyzer and the TA-TCA Tablet Coating Adhesion Fixture are designed to measure how well the coating adheres to the surface of a tablet. The fixture compresses the tablet firmly between double-sided sticky tape on both probes and measures the negative load required to pull the coating from the tablet as the upper probe retracts. **Brookfield Engineering Laboratories,** *Middleboro, MA • www.brookfieldengineering.com • tel. 800.628.8139*

Filter assembly

The UltraSnap filter assembly is a configurable system that secures multiple pre- and final filters into a single-use filtration system. The assembly features one inlet and outlet connection for immediate deployment. The customizable system allows maximum flexibility in design to accommodate end-user processing requirements for flow capacity, throughput volume, and retention efficiencies. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

UL-rated stainless-steel control panel

Ross SysCon, a worldwide supplier of process control and automation systems, builds UL-rated stainless-steel control panels of virtually any size or complexity. The system contains a stainless-steel enclosure for soft start and variable speed control. A 4-in. color touch screen is mounted on the panel door for control and viewing of agitator speed, load, cycle time, and forward/reverse agitator direction. **Ross SysCon,** *Savannah, GA • www.mixers.com • tel. 912.238.5800*

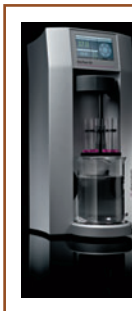
MANUFACTURING EQUIPMENT & SUPPLIES

Automated filling, plugging, and capping system

Flexicon's FPC50W is an operator-friendly, fully-automated filling, plugging, and capping system, offering accuracy and flexibility for aseptic filling in clinical trials and scale-up applications. The FPC50W is equipped with a Wipotec weighing cell, which measures the weight of each individual fill with an accuracy rate of +/-0.002 g, handling filling requirements with peristaltic aseptic filling technology from 0.1 to 100 mL fill sizes. **Watson-Marlow Pumps Group,** *Wilmington, MA • www.wmpg.com • tel. 800.282.8823*

Nanofiber filters

Sartoguard NF filters use nanofiber technology to provide ultrafine particle and contaminant retention as well as high flow rates. The filters are purposed for a range of biopharmaceutical filtration applications, and are designed to provide optimal protection of sterilizing-grade and mycoplasma-retentive filters for high efficiency and economy. In addition, the filters contain polyethersulfone membranes intended to enhace total throughput performance. **Sartorius Stedim North America,** *Bohemia, NY • www.sartorius.com • tel. 631.254.4249*



Disintegration testing system

Pharmatron's new DisiTest 50 automatically detects the disintegration time of each tablet/capsule and prints a detailed report. The system is fully compliant with USP regulations and contains induction heating technology, reducing heating time to 3–5 min. and eliminating time-consuming cleaning tasks associated with a traditional water bath. **Pharmatron,** *Manchester, NH • www.pharmatron.com • tel. 603.645.6766*

MANUFACTURING EQUIPMENT & SUPPLIES

Handheld analyzer

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

Moldable, weldable, sealable tubing

AdvantaFlex biopharmaceutical tubing is moldable, sterile weldable, and heat sealable. When molded into single-use manifolds, it eliminates many barbed fitting connections and their risk for leaks and contamination. The tubing contains no silicone oils or animal-derived ingredients. Validation and extractables test portfolios are available, as well as validated sterility assurance. **AdvantaPure,** *Southampton, PA • www.advantapure.com • tel. 888.599.6099*

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BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies to support their commercialization objectives by offering unique drug delivery systems and a variety of sterile contract manufacturing form/fill/finish services and solutions for injectables designed to meet complex and traditional sterile manufacturing challenges. **Baxter BioPharma Solutions,** *Deerfield, IL • www.baxterbiopharmasolutions.com • tel. 800.422.9837*

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Kemwell Biopharma is contract provider of CMC services to the pharmaceutical and biotechnology industry. With manufacturing locations in Bangalore, India, and Uppsala, Sweden, Kemwell offers services ranging from formulation development, analytical services, clinical manufacturing, commercial manufacturing, and packaging/storage/distribution services. **Kemwell Biopharma,** *Research Triangle Park, NC • www.kemwellbiopharma.com • tel. 919.397.3000*

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Irvine Pharmaceutical Services

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

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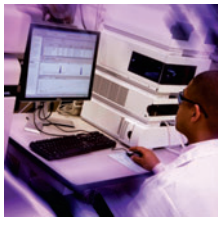
The Dow dermatology and ophthalmic drug-development teams provide clear strategies to guide drugs, biologics, or medical devices through the regulatory approval process. Dow's staff has decades of experience successfully managing nonclinical, clinical, and regulatory programs for several pharmaceutical,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



Bioanalytical analysis

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

CLEANROOM EQUIPMENT & SUPPLIES

Laboratory cleaning system

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

Mop frame

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

PACKAGING EQUIPMENT & SUPPLIES

Blow–fill–seal machine

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

PACKAGING EQUIPMENT & SUPPLIES

Packaging solution

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

Transfer packaging for prefillable syringes

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

LABORATORY EQUIPMENT & SUPPLIES

Thermal sterilizers and pasteurizers

MTIBioPharm continuous thermal sterilizers and pasteurizers (kill and viral inactivation systems) are designed to offer superior and more consistent product quality liquid pharmaceuticals and growth media compared to traditional thermal processes, such as retorts. The units are intended to reduce costs and risk, while increasing product quality. **MicroThermics,** *Raleigh, NC • www.mtibiopharm.com • tel. 919.878.8045*

LABORATORY EQUIPMENT & SUPPLIES

On-line TOC analysis

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

Laboratory blenders

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

Process analytical sensors

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

LABORATORY EQUIPMENT & SUPPLIES

Anion exchange column

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

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INFORMATION TECHNOLOGY

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Model-predictive control

Various control systems can be implemented on the flowsheet model in the form of simple PID loops (7) or with advanced model-predictive control (MPC) (9). Control loops can be implemented by identifying the control-loop pairings and assessing the need for MPC in each control loop (as opposed to using just PID loops). With this information, the PID controllers are designed and implemented to obtain a predictive model of the plant, thereby suggesting the design of the MPC controller. The designed MPC is then incorporated into a general model for model-based performance evaluation.

As an example, consider integration of control hardware and software in the continuous feeder and blender system. A process analytical technology (PAT) system is used to read the near-infrared (NIR) spectral data at the blender outlet and communicate it to the multivariable analysis (MVA) model performing principle-component analysis and partial least-squares (PCA/PLS) to provide the API concentration and relative standard deviation (RSD) value. These critical quality attributes (CQAs) are used as inputs to the MPC in the process-control system. The MPC uses the two CQA inputs to drive the feed ratio and the blender speed. The MPC output (feed ratio) gives the feeders' flowrate setpoints, which are then tracked by slave PID controllers. The implemented control scheme utilizes a PAT data-management system (synTQ, Optimal) to integrate a digital automation system (DeltaV, Emerson Process Management) with an NIR analyzer and MVA model. (For a visual of this system, see the online version of this article at pharmtech.com/MPC.) Integrating multiple system parts presented several challenges. A framework, however, is now in place that allows implementation of control architectures for a wide variety of continuous powder processes.

Acknowledgements

This work is supported by the National Science Foundation Engineering Research Center on Structured Organic Particulate Systems, through Grant NSF-ECC 0540855.

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Ad Index

The EU Changes Guidelines for Good Distribution Practices

Siegfried Schmitt discusses the European Commission's (EC) guidelines on *Good Distribution Practice of Medicinal Products for Human Use*, published March 7, 2013 (2013/C 68/01). This document replaces the previous version from 1994. This new GDP guideline applies not only to the wholesalers and manufacturers of pharmaceuticals, but also brokers. The guideline comes into force on September 8, 2013.

Q. Are there any significant new requirements in the EC's guideline?

A. The main body of changes affects wholesalers and brokers; the 1994 guideline only referred to wholesalers. Wholesalers must be licensed and brokers must be registered in a Member State of the European Union. The regulations go even further, requiring that brokers must have a permanent address and contact details in the Member State where they are registered.

Q. Does that mean companies can no longer use a broker in Switzerland?

A. Unfortunately no, unless the broker also has a permanent address in an EU Member State and is registered there.

Q. What are the key changes for wholesalers?

A. The role of the responsible person has been defined in much more detail. This is a role comparable to the head of the quality unit. The regulation specifies that the responsible person should fulfill their responsibilities personally and should be continuously contactable. The responsible person is only allowed to delegate duties, but not responsibilities. Moreover, this expert should have a degree in pharmacy. No explanation is given for this peculiar expectation, nor is it made clear what acceptable alternatives may be. Few companies employ a pharmacist as wholesale and distribution is not a classical field of expertise for pharmacists.

Q. Have there been any significant changes affecting warehouses?

A. Yes, with regards to storage and segregation, and computerized systems. The standard requirements for restricted access and segregated areas for medicinal products can still be complied with through physical segregation or by means of a validated computerized system. However, medicinal products received from a third country, but not intended for the EU market, have to be physically segregated. The same requirement for physical segregation now also applies to expired products.

A computerized system needs to be validated or its fitness for purpose demonstrated through verification studies. What constitutes appropriate verification studies though remains a total mystery. It is accepted practice that quality relevant records need to be retained for certain periods of time. Why the authors of this guideline decided to codify that backup data (but, not the records) are to be retained for a minimum of five years at a separate and secure location is another unexplained mystery. Backups are generally kept for a week by which time they have become obsolete.

Q. Despite all the above, the guideline surely strengthens compliance and strengthens supply-chain security?

A. Without a doubt, the guideline has been long overdue and is welcomed by industry and regulators alike. Requiring wholesalers and brokers to be licensed or registered, and to also have a comprehensive quality system in place, is a great step forward. It is not yet clear to what extent these companies will be in a state of compliance by September, if the Member States will have the necessary administrative processes in place (e.g., for broker inspections and registration), and if these tightened regulations may lead to certain drug shortages. The pharmaceutical industry will also have to amend their procedures, as they must assure that in future they will only use appropriately licenced/registered and compliant wholesalers and brokers. As with all new regulations, teething problems may be expected, but overall it will strengthen supply-chain security and patient safety. **PT**

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