MARCH 2013 Volume 37 Number 3

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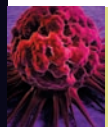

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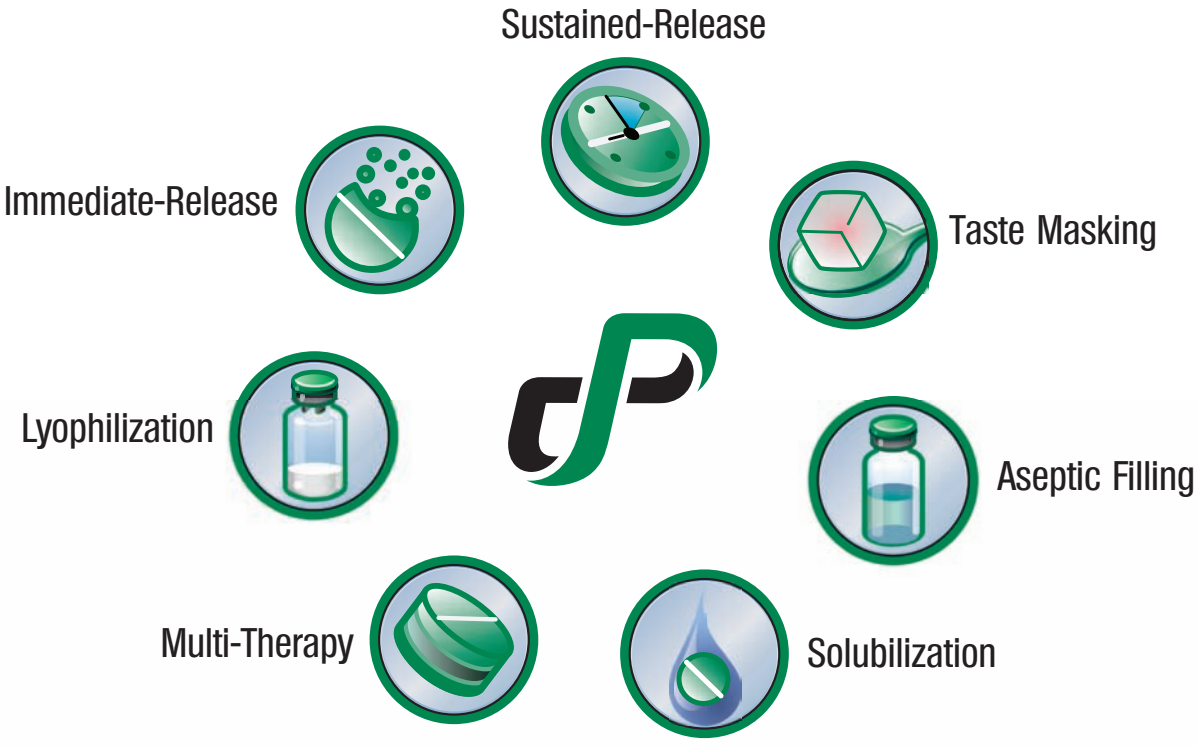

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Pharmaceutical Technology is the authoritative source of peer-reviewed research and expert analyses for scientists, engineers, and managers engaged in process development, manufacturing, formulation and drug delivery, API synthesis, analytical technology and testing, packaging, IT, outsourcing, and regulatory compliance in the pharmaceutical and biotechnology industries.

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On the cover

COVER STORY

38 PAT for Parenteral Drug Manufacturing

Applying quality-by-design and process analytical technology facilitates process understanding and control of various operations in lyophilization.

Illustration by Dan Ward
Images: JurgaR/Getty Images

FEATURES

DEPARTMENTS/ PRODUCTS

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PEER-REVIEWED RESEARCH

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SUPPLEMENT

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Being a single parent has presented its challenges, but there's nothing I wouldn't do for my girls.

I've worked at Jubilant Hollister-Stier for 17 years and the people there are like family to me. That's why I wouldn't trust anyone else to manufacture my blood pressure medication.

Jayda and Mallory don't think about how that tiny pill helps keep their dad healthy, but I do.

Jayda and Mallory's dad is a JHS employee

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Catching Up

Rita Peters

A quality-by-design paradigm advances process understanding in development and manufacturing.

When Galileo Galilei gained fame more than 350 years ago as a physicist, mathematician, and astronomer, his theories placed him ahead of other thinkers of the time. His contributions to observational astronomy in support of heliocentrism—that the Earth revolves around the sun—made him a controversial figure in his time.

One of Galileo's observations, "By denying scientific principles, one may maintain any paradox," supported his belief in science-based studies and rings true for pharmaceutical and biopharmaceutical development and manufacturing today.

True to Galileo's words, in this issue, we focus on what has become an overarching thrust to biopharmaceutical/pharmaceutical development and manufacturing, namely the application of a science- and risk-based approach under quality-by-design (QbD) principles. Process analytical technology (PAT) is key element of QbD for achieving process understanding, and we examine the advances in PAT as it applies to parenteral drug manufacturing.

We also examine, in a roundtable of industry experts, the implementation, including the challenges, of process validation in line with the product lifecycle concept underlined in FDA guidance and ICH guidelines.

Analytical testing and instrumentation, which underpins all development and manufacturing, is an integral part of achieving the desired product quality not only in a QbD paradigm but also for "traditional" development and manufacturing.

In mid-March, analytical scientists from around the world will gather in Philadelphia for the Pittcon conference and exhibition, billed as the largest meeting for the analytical sciences.

By denying scientific principles, one may maintain any paradox.

The program covers advances in analytical methods development, testing, and instrumentation using chromatography, spectroscopy, electrochemistry, microscopy, thermal analysis, and other techniques. Conference programs will detail novel applications of measurement science for pharmaceuticals, biomedicine, nanotechnology, and more. The editors of *Pharmaceutical Technology* will be in attendance, exploring the latest advances in analytical technology.

An introduction

In late January, I joined Advanstar Communications as editorial director for the Pharmaceutical Drug Development and Manufacturing Group. In that role, I oversee *Pharmaceutical Technology, Pharmaceutical Technology Europe*, and *BioPharm International.*

I am excited to work with the editorial team: Executive Editor Patricia Van Arnum, Managing Editor Susan Haigney, *PharmTech Europe* Editor and Scientific Editor Adeline Siew, Scientific Editor Amy Ritter, Manufacturing Editor Jennifer Markarian, and Community Editor Christopher Allen.

Although new to these publications, I previously worked for a publication in the drug-discovery segment of the pharmaceutical industry. I also have worked on publications addressing contamination control and controlled environments.

I look forward to the challenge of providing readers with the research, technical insight, and expert analysis needed to advance formulation and drug delivery, API manufacturing, finished drug-product manufacturing, analytical testing, and regulatory compliance. *Pharmaceutical Technology* will continue to deliver peer-reviewed research and technical articles in print, as well as news, expert analysis, and interviews on *www.PharmTech.com*. Our weekly *ePT* newsletter, and monthly S*ourcing and Management* and *Equipment & Processing* newsletters, deliver news and exclusive features directly to your desktop. In the coming months, we will be expanding our interactive features of podcasts, webcasts, polls, and exciting new media products.

Interaction with our readers is of utmost importance. We welcome your comments, thoughts, suggestions, and editorial contributions. **PT**

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

HITTING THE HEADLINES

FDA Lists Guidance Documents Planned for 2013

FDA has released a list of more than 50 guidance documents planned for 2013. Planned documents include, among others, *Quality Systems Approach to Pharmaceutical cGMP Regulation*, *Uniformity of In-Process Mixtures, and Control of Highly Potent Compounds*, as well as guidance relating to biosimilars.
PharmTech.com/FDA2013

European Commission Investigates J&J and Novartis

The European Commission (EC) claims that Johnson & Johnson and Novartis may have breached European antitrust rules. According to the EC, an agreement concluded between the companies' subsidiaries may have delayed the market entry of generic versions of the painkiller fentanyl in the Netherlands.
PharmTech.com/ECInvestigates

Ben Venue Laboratories Enters Consent Decree

Venue Laboratories has entered into a consent decree with FDA over violations of cGMP. Under the terms of the consent decree, Ben Venue is still permitted to manufacture and distribute more than 100 drugs that are essential for patient care.
PharmTech.com/BenVenue

Lilly Ends Phase III Trial

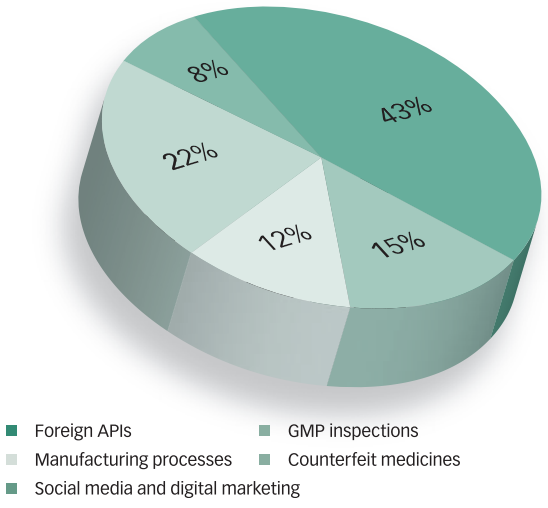
Eli Lilly and Co. has discontinued its Phase III rheumatoid arthritis programme for tabalumab, an anti-BAFF (B cell activating factor) monoclonal antibody, because of lack of efficacy. The decision was not based on safety concerns.
PharmTech.com/LillyTrial

INDUSTRY NEWS

- Patheon is planning additional investment in its Milton Park facility located in Oxfordshire, United Kingdom.
- Elan Corporation, through its wholly owned subsidiary, Elan Science Three Limited, has agreed to sell all of its remaining 7.75 million ordinary shares of Alkermes through Jefferies & Company.
- AAIPharma has expanded its laboratory service offerings, capabilities and instrumentation at its laboratory technology centre in Wilmington, North Carolina.
- GlaxoSmithKline has increased its stake in its Indian subsidiary, GlaxoSmithKline Consumer Healthcare Ltd, from 43.2% to 72.5%.

READERS THINK THAT...

What area do you think will see increased regulatory attention and enforcement in 2013?



View more poll results at:
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MOST TWEETED

- Report says anticompetitive activity in #pharma industry is increasing ht.ly/h7MPt
- More outsourcing expected in the world of pharma and biopharma in coming years ht.ly/gTfgG
- Lonza pumps cash into pharma manufacturing expansion in Switzerland ht.ly/gQVSx
- Pfizer reveals pharma financials. Revenues fall 7% in Q4 2012 compared with 2011 ht.ly/hqFxn
- Pharma innovators: J&J comes top in a report. Amgen, Roche, Merck and Sanofi came 2-5 respectively ht.ly/hqF3Q

LINKEDIN DISCUSSION POINTS

The European Commission has published the revised Chapter 8 on Complaints, Quality Defects and Product Recalls. The chapter has been revised completely.

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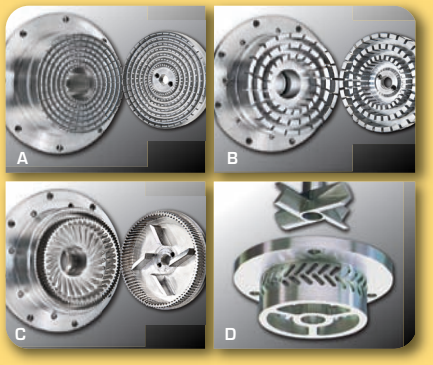

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Editors' Picks of Pharmaceutical Science & Technology Innovations

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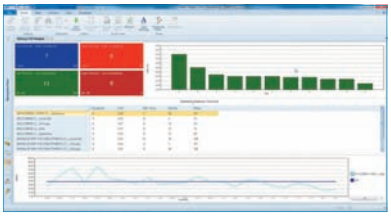

Updated process optimization software offers usability enhancements

The latest version of Aspen Technology's aspenONE software (V8) provides new functionality, and usability and visualization enhancements. For manufacturing and supply chain purposes, the software features adaptive process control, which automates many tasks and makes maintenance a continuous process. The software also includes the company's Aspen Collaborative Demand Manager, which provides information to help manage different forecasting requirements. Other features include energy and economic analysis and solids modeing functionality.

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Technology offers nucleation process control in freeze drying

SP Scientific's ControLyo Nucleation On-Demand Technology can be retrofitted to range of previously installed production freeze dryers and can help to make the freezing step more repeatable. The random nature of nucleation has often prevented the freezing step of lyophilization from being controlled, but SP Scientific's technology helps to regulate the nucleation temperature. As well as offering greater control over cycle optimization, the technology can also help improve vial-to-vial uniformity, reduce cycle times, reduce protein aggregation and enable easier process scale-up. In addition, the technology can help lyophilization processes to adhere to process analytical technology and quality-by-design initiatives.

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Relevance Regained

Simon Chalk

Companies risk drowning in alphabet soup if the latest three-letter acronym improvement strategy isn't clearly linked to business strategy.

While other industry sectors have adopted prepackaged improvement programs since the 1980s, it is only in the past decade that the biopharmaceutical industry has witnessed the rise to prominence of the three-letter acronym (TLA)-based improvement initiative. Business process management (BPM) and human error reduction (HER) are currently in vogue. While much has been promised by these prescribed solutions to improve business performance, much of this promise has proved illusory. Even where measurable improvement has been achieved, it has not always shown where it matters in overall operational performance and on the bottom line.

The truth is that while most of these approaches do have intrinsic value, unless the approaches are rigorously adapted to the situation of the business and the needs of strategy, the results are unlikely to be what is required. Many managers intuitively know from their own experience that just improving things without a clear link to strategy will not necessarily produce better business results. In some companies, the problem has been exacerbated by changes in priorities and direction caused by the switch from one TLA to another, as disillusion with the previous approach has set in. A few unfortunate organizations have nearly drowned in the resulting alphabet soup.

Change needs to be focused on delivering the business strategy. It is through realizing the strategy that the company gains competitive edge, and it is this that delivers the bottom line. Moreover, for the biopharmaceutical industry, GMP compliance needs to be up front and center along with productivity and service.

Many improvement programs do not derive their change agenda directly from the business strategy but come complete with their own. Too often, this leads to change being driven by the dictates of the approach, not by the needs of the business. Things frequently end up being done because the selected approach says "it's a good thing" and not because improving the way a particular task is done is essential for the company to deliver its strategy. As a result, precious resources can be diverted away from the important things.

There are no simple solutions or short cuts to improved business performance, but there are some fundamentals upon which a pragmatic, strategy-directed change program can be built.

- Provide the organization with leadership.
- Clearly communicate the values and guiding principles that underpin the strategy and make them real in the form of the appropriate behaviors, policies, performance measures, and reward and recognition systems.
- Concentrate on bringing people along and gaining their commitment to the actions that have strategic significance.
- Make sure the basics are in place before becoming more ambitious. It is important to build sound processes, habits, and capabilities into the business to avoid the risk of building on sand.
- Direct the improvement where it gives maximum impact in delivering the business strategy by targeting the actions that are key to achieving operational excellence and GMP compliance.
- Make sure that the organization is capable of handling the load being placed upon it. Over-stretching an organization disproportionately reduces effectiveness and generally results in nothing getting done properly.
- Invest in training and development to raise the overall capability of the business and particularly those capabilities that support the core competencies.
- Assess each technique, theory, and approach rationally in terms of problems it can solve. After careful consideration, discard what is not useful and adapt what remains to suit the needs of the situation.
- Test and refine solutions through experimentation and be prepared to learn from minor mistakes.
- Never lose sight of what you are trying to achieve.

To perform over the long term, the winners will be those companies that can most effectively deliver their strategies. Any change initiative that is not directed by the requirements of the strategy and tailored to the needs of the business is unlikely to succeed because it will lack true relevance. It is only by creating a clear link with strategy and following through with a pragmatic approach to implementation that a company makes the best of its strategy and thereby gives itself the best chance of success. **PT**

Simon Chalk is director of the BioPhorum Operations Group, simon@biophorum.com.

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REGULATORY **ROUNDUP**

Identifying quality

When drugs and biologics are in short supply or carry high prices, physicians and other providers appear willing to purchase medicines from unknown sources, ignoring the possibility that those products might be adulterated, counterfeit, or ineffective. One response from FDA officials is to devise a method for identifying products that meet quality standards. If such a designation translated into higher sales, that would prompt manufacturers to invest more in improving production facilities, particularly those that make sterile injectable products, according to Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), and Marta Wosinska, director of CDER's economics staff. Writing in "Clinical Pharmacology and Therapeutics," the regulators describe how generic-drug makers compete on price, and not quality, because purchasers consider all generics equally effective and safe and often cannot link safety problems to specific products or patients (1). Thus, the market fails to reward product quality and encourages manufacturers to reduce costs by minimizing investment in quality production. FDA's proposal is to provide buyers and payers with "meaningful manufacturing quality metrics," similar to quality measures used to grade restaurants, create HMO scorecards, or identify vitamins that meet United States Pharmacopeia criteria.

More counterfeits

Despite all the publicity and alerts warning against the purchase of fraudulent and unapproved medicines, FDA recently uncovered more fake versions of Roche's cancer drug Avastin (bevacizumab) circulating in the US healthcare system. The drug is being distributed by Medical Device King (also known as Pharmalogical), and lab tests show that some batches have no active ingredient. FDA admonished doctors to be wary of medicines carrying deep discounts that appear "too good to be true." They're probably counterfeit, and the federal government is putting distributors in jail and bringing charges against physicians who knowingly buy the drugs.

Help with better labels

An FDA rule adopted in 2006 called for manufacturers of drugs and biologics to update the labeling on new and recently approved products so that prescribing information is clearer and more useful for health professionals. Unfortunately, only 15% of all drugs and biologics have adopted the Physician Labeling Rule (PLR), largely because it only applies to therapies approved after June 2001. Generic drugs get a pass, moreover, unless the innovator changes its label, which has not occurred for many older products where brands are no longer on the market. To spur broader adoption of the PLR format, CDER is offering to provide manufacturers with draft PLR labeling and assistance in converting to the new labeling format. CDER announced the proposal in the Feb. 6, 2013 *Federal Register* and seeks comments on how best to help industry with labeling conversion (2).

Real-time safety surveillance

FDA is building on its Mini-Sentinel system for monitoring the safety and performance of drugs after the drugs come to market by shifting to the full Sentinel System envisioned by 2007 FDA legislation. The plan is to establish a "sustained active surveillance system" that can serve as a "national resource" for assessing multiple healthcare issues, explained CDER's Janet Woodcock at the 5th Sentinel Initiative Public Workshop in January 2013. Mini-Sentinel has operated through a distributed database model that obtains answers to drug-safety questions from a network of healthcare data systems. Over the past five years, the program has established core operations, research methods, and protocols for testing drug safety evaluations. With the expiration of the mini-sentinel program at the end of 2014, Woodcock envisions a broader consortium, which may include pharmaceutical manufacturers that can access data from the current system and additional sources to support product quality. Further methodological research will explore ways to ensure that results from Sentinel operations are valid and that Sentinel supports "the public good."

Sunshine at last

The aim of the long-awaited federal "Sunshine" rule, issued Feb. 1, 2013 by the Centers for Medicare and Medicaid Services (CMS), is to prevent undue industry influence on prescribing and biomedical research by requiring manufacturers to report all payments and "transfers of value" to physicians and teaching hospitals. Enacted as part of the Affordable Care Act (ACA) of 2010, the Sunshine program took nearly two years to finalize, largely because doctors protested that disclosure of payments from pharmaceutical and medical device companies would be misleading and taken out of context. The final rule sets timeframes and specifics for manufacturers to file information with CMS on payments for research activities, consulting fees, gifts, meals, travel costs, and speaking fees, plus ownership and investment interests of a doctor and his family in an "applicable manufacturer." CMS gave doctors a few extra days to review and challenge industry data before posting the data on its website, and manufacturers are expected to avoid such disputes by establishing electronic "aggregate spend" tracking systems that permit them to share and confirm payment data with recipients prior to CMS filing. With all the delays, manufacturers now have until March 2014 to report payment data for August through December 2013, and the data won't be posted until September 2014. It remains to be seen if "Sunshine" discourages physicians from serving as investigators in commercial clinical trials or as consultants or advisors to manufacturers.

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Vaccine Innovation Yields New Products and Processes

Vaccine development is benefiting from manufacturing advances and support for global health.

There is great enthusiasm for developing new vaccines to combat debilitating diseases, which is spurring improvements in analytical methods and production strategies that are more efficient and provide greater assurance of product quality. Vaccine production has become more attractive to pharmaceutical manufacturers seeking new products to help offset the decline in revenues and profits from patent expirations on blockbuster therapies. Although vaccines may not be big moneymakers for biopharmaceutical companies, vaccines can produce solid revenues by providing highly cost-effective treatments for stable markets.

There also are strong moral and public health reasons for industry investment in treatments that can prevent the spread of infectious diseases and new pathogens. The World Health Assembly approved a 10-year Global Vaccine Action Plan in May 2012 to develop and distribute more new preventive drugs around the world, with Dengue fever and malaria at the top of the list of targeted illnesses. Research on vaccines to treat global diseases also may lead to more lucrative preventives against widespread conditions such as cancer and other diseases caused by viruses, bacteria, or parasites. Two approved vaccines that prevent cervical cancer are on the market, Merck's Gardasil and Cervarix from GlaxoSmithKline, along with the first cancer treatment vaccine, Dendreon's Provenge, for metastatic prostate cancer.

The challenges in devising safe and effective vaccines, however, are all too apparent. Years of research have failed to produce a vaccine to prevent HIV/AIDS. Therapeutic vaccines are proving elusive, as seen in difficulties using vaccine technology to treat nicotine addiction, diabetes, and Alzheimer's disease. A notable disappointment is the recent failure of a promising tuberculosis vaccine following a study

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on almost 3000 South African infants. Scientists at Oxford University, vaccine maker Aeras, the Wellcome Trust, and the Bill and Melinda Gates Foundation tried to sound positive in announcing the results, stating that important evidence was obtained from this model, placebo-controlled trial, and that the vaccine still might be effective in adults.

More new vaccines

At the same time, there is much good news in the vaccine world. This year started with FDA approval of wider use of Pfizer's Prevnar 13 vaccine to prevent pneumococcal bacterial infections. That followed approval in 2012 of Glaxo's MenHibrix, a combination vaccine to protect against meningococcal and Haemophilus influenzae type b (Hib).

Notable advances in formulations and manufacturing processes for influenza vaccines have attracted considerable attention in this year's more severe flu season. The flu vaccine crop of 2012 included two quadrivalent products (i.e., vaccines that protect against four virus strains instead of three) from Glaxo and AstraZeneca.

Manufacturers, moreover, are shifting away from producing flu vaccine in chicken eggs, as seen in FDA approval in November 2012 of Novartis' Flucelvax, produced in cultures of dog kidney cells. It will be scaled up at Novartis' new vaccine plant in Holly Springs, NC, built with some $500 million in support from the US government. Similarly, Protein Sciences Corp. (Meriden, CT.) gained FDA approval in January 2013 for FluBlok, which utilizes recombinant DNA technology to produce large quantities of flu virus protein using an insect virus (baculovirus) expression system. Protein Sciences also has benefited from more than $100 million in federal funding and plans production at a former Pfizer manufacturing site in Pearl River, NY.

Many of these advances reflect increased US government investment in vaccine production methods since 2006 when the Department of Health and Human Services (HHS) provided more than $1 billion to six manufacturers to develop cell-based flu vaccine technology and production capacity in the US that can ramp up production quickly in case of pandemic or other health crises. The looming H1N1 swine flu fear in 2009 added funding to expand domestic vaccine production, and in 2012, HHS provided $400 million to three research consortia to further enhance production of vaccines and medical countermeasures. HHS assistant secretary Nicole Lurie noted, in an HHS press release, that the three public-private partnerships—which include Glaxo, Novartis, and Maryland-based Emergent BioSolutions; academic research centers; and small biotech companies—will use the funds to retrofit existing facilities or build new ones with "flexible, innovative manufacturing platforms that can be used to manufacture more than one product."

A cadre of other new vaccines is in the works. Novartis recently obtained approval in Europe for a new vaccine against meningitis B, while Glaxo has linked up with an Indian manufacturer to develop a six-in-one combination pediatric vaccine. Baxter has another cell-based vaccine for avian flu on the market in Europe, and genetically engineered flu vaccines are being tested by Novavax (Rockville, MD) and Vaxinnate Corp. (Cranbury, NJ). A long-term goal is to develop a universal flu vaccine that fights multiple virus strains and can be administered every 5 to 10 years. There also is promising research on new vaccine delivery technologies and products that don't require cold-chain distribution.

Analytical advances

Continued progress involves addressing difficult vaccine quality and safety issues, as discussed at the January 2013 WCBP symposium in Washington, DC, sponsored by CASSS and FDA. Scientists noted the need to "solve the riddle" of how to make these complex products at moderate cost using modern biotechnology. This progress involves defining the range of acceptable variability in characterizing these inherently heterogeneous products, including release and stability data that reflect both process/analytical capability and biological suitability of the final product. Participants in a WCBP vaccine workshop further explored issues in achieving manufacturing control and in defining critical attributes for newer vaccines. There was discussion about strategies for designing appropriate potency assays, for setting release and stability specifics, and for justifying a range of variability with available clinical data. Concerns that some newer, highly purified vaccines may appear less efficacious than older, heterogeneous products illustrate a need for clear potency assays.

The importance of harmonization in national vaccine regulatory policies was emphasized at the December 2012 PDA/FDA vaccine conference in Bethesda, MD, which also examined issues related to expanding global access to effective vaccines. Leading vaccine makers expressed frustration with frequently changing standards, data requirements, approval processes, and policy interpretations by regulatory authorities around the world. Manufacturers would like to see a functional "mutual recognition" process for vaccine market approvals, or perhaps a global body that reviews standardized data for all markets. The vaccine industry is working closely with the world health community to greatly expand access to crucial vaccines for millions of children around the world, a goal that would benefit from regulatory processes able to identify products that do and don't meet quality standards, as well as an international process for identifying and monitoring vaccine safety problems.

Further research also is needed to address still prevalent "anti-vaccine" fears held by many parents and patients. A report issued by the Institute of Medicine (IOM) in January 2013 confirmed the safety and benefits of the US childhood immunization schedule and advised against moves by parents to stretch out or delay childhood vaccination (1). Even so, immunization rates in most states fall below the desired 95% level and are even worse in Britain and many other countries. Manufacturers need to join with the health community to support research on still-prevalent fears about vaccination and to bolster evidence on the critical benefits of immunization.

Reference

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Europe and the United States to Negotiate a Free-Trade Agreement

Discussions are underway as the pharmaceutical sector calls for greater consistency in the global monitoring of GMP compliance and quality testing of APIs and finished medicines.

Producers of APIs in both Europe and the United States are hoping that a European Union (EU)-US free-trade agreement would provide a platform for the creation of a system for the global monitoring of standards of GMP. The agreement aims to dismantle barriers of transatlantic trade, particularly nontariff measures (e.g., the provision of safety certificates or evidence of quality compliance) that have generated conflicting regulatory regimes. Negotiations are expected to start this year.

A study by the Dutch consultancy, Ecorys Nederland BV based in Rotterdam, funded by the European Commission (EC), estimated that an agreement could potentially reduce trading and investment costs in pharmaceuticals by 15.3% for US companies and by 9.5% for EU companies. The pharmaceutical sector in the EU and US hopes that, with this free-trade agreement, there would be greater consistency in areas such as regulations on GMP compliance as well as quality testing of APIs and finished medicines using pharmacopoeia standards. Once in operation, the agreement is expected to provide the pharmaceutical sector on both sides of the Atlantic with the basis for a robust system for GMP inspections of API plants throughout the world. These inspections could be done initially by joint teams of inspectors from the EU and the US, together with those from other developed countries such as Japan and Australia.

There are, however, signs that preliminary talks between EU and US officials are running into problems. The publication of a report by a high-level working group, given the task of recommending proposals to be discussed in the negotiations on the deal, has been delayed at least three times. Within the pharmaceutical sector itself, the EU has erected new nontariff barriers and taken measures considered to be inconsistent with international GMP standards, all of which are seen as possible obstacles to a successful outcome of the discussions.

Recently, the EU has been taking steps to strengthen checks on GMP compliance of imported pharmaceuticals while extending the scope of its GMP rules. This effort is reflected in the details of the Falsified Medicines Directive (FMD), an EU legislation aimed at combating counterfeit medicines that includes provisions for closer scrutiny of API quality. For example, a controversial section of the FMD's regulations stipulates that imports of active substances into the EU must be accompanied by written confirmation from the exporter's national regulatory authority that the plant manufacturing the API complies with GMP standards equivalent to those in the EU. This requirement is due to come into effect on July 1 this year; however, some countries will be exempted from it on the grounds that they have systems in place for regulating and monitoring GMP standards that are equivalent to those in the EU.

The US, through FDA, is one of several countries that has applied to be assessed for exemption from the need for providing written confirmations. "We do count on the EU to put every effort into completing its US assessment in a timely fashion to allow sustained US-made API importations and sustained EU-based medicines production using these imports," says Julie Marechal-Jamil, senior manager, quality and regulatory affairs at the European Generic Medicines Association (EGA), Brussels.

We have big concerns with the FMD because it has the potential to be a trade barrier.

The FMD also confirms the EC's intention to extend GMP to the starting materials used in the manufacturing of APIs. For example, active substance manufacturers would be required to check out claims by suppliers about the sources of their starting materials. Some European pharmaceutical companies have protested that these new rules on starting materials exceed the EC's own GMP guidelines.

"We have big concerns with the FMD because it has the potential to be a trade barrier," says John DiLoreto, executive director of the Bulk Pharmaceuticals Task Force (BPTF) of the Society of Chemical Manufacturers and Affiliates (SOCMA), Washington, DC. "We need to get as much international harmonization as possible with GMP. The European Commission and the FDA have got to a point where there is not much distance between what they want. The EU then comes up with the FMD, which requires the FDA to be exempted from the written confirmation rule."

The EC insists that it is not putting up new nontariff barriers or working outside the Q7 rules on GMP for APIs drawn up by the International Conference on Harmonization (ICH). "These claims are completely unsubstantiated," says a Commission spokesperson. She stressed that the introduction of equivalence regulations in the FMD, such as the written confirmation requirement, are consistent with the rules of the World Trade Organization while the EU's GMP standards remain "equivalent" to ICH Q7 standards and GMP standards of the World Health Organization (WHO).

Joint proposals for the EU-US trade agreement by the European and US producers of APIs are focused mainly on

the issue of GMP compliance. Three of the four proposals, put forward in a joint statement in Oct. 2012 by SOCMA, the European Fine Chemicals Group (EFCG), and the Active Pharmaceutical Ingredients Committee (APIC) of the European Chemical Industry Council (Cefic), deal with GMP certification, a mutual recognition agreement of GMP inspections, and regulatory assessments of process changes. The fourth proposal focuses on the need for transatlantic harmonization of pharmacopoeia to provide more impetus to the establishment of a global pharmacopeia standard.

On the matter of GMP certification, the joint statement emphasized the necessity of reconciling FDA's system of giving manufacturing sites "certificates of pharmaceutical product" with the EU's detailed confirmation of GMP standards. With systems on reporting of process modifications, there is also a need to resolve differences between the EU and US relating to what process changes need to be reported to licensing authorities and whether they should be reported before or after the changes are implemented. With respect to a mutual recognition agreement between the EU and the US that was first discussed in the late 1980s, the three trade organizations (SOCMA, EFCG, and APIC) argued it would enable EU and US agencies to concentrate their efforts on GMP inspections in third countries.

Even without the EU-US free-trade initiative, progress is already being made in bilateral cooperation across the Atlantic on key issues. A four-year-old joint-plant-inspection program between FDA and EMA entered a second phase last year but is still being limited to a few sites. "At least there are stakes being placed in the ground, which ought to move things forward," says Tony Scott, adviser to the EFCG. Since 1989, the European Directorate for the Quality of Medicines (EDQM), which is responsible for the European Pharmacopoeia, and its US counterpart the United States Pharmacopeia (USP) have been drawing up mutually recognized monographs on drugs. Both are participating in a scheme, launched last year by WHO, for global pharmacopoeia standards. "Out of a total of 2200 monographs, we and the USP have so far harmonized less than 100," says Susanne Keitel, EDQM secretary. "Harmonization entails a lot of hard work."

For the EU–US free-trade negotiations, the major target will be to achieve a mutual recognition agreement because of its implication for worldwide recognition of inspections. "The talks on the transatlantic trade agreement has given us an opportunity to reopen dialogue to try to achieve an EU–US mutual recognition agreement," says Scott. "If successful, it could be the first in a series to eventually cover the global pharmaceutical industry." The vision is for the global pharmaceutical industry to have a global GMP inspection system. Perhaps the EU–US free-trade deal would kick start crucial moves towards realizing it. **PT**

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Conforming to the IPEC CoA Guide

Past IPEC-Americas excipient qualification committee chairs highlight changes to the IPEC guide on certificates of analysis for bulk excipients.

More than a decade has elapsed since the *IPEC-Americas Certificate of Analysis Guide for Bulk Pharmaceutical Excipients* (CoA Guide 2000) was published (1). Since then, important changes in the global pharmaceutical industry and regulatory arena have occurred, which have necessitated development of the *IPEC Certificate of Analysis Guide for Pharmaceutical Excipients*, 2013 (CoA Guide). Among those changes are the formation of the IPEC Federation in 2010, publication of interrelated IPEC documents (2-12) that reference excipient certificates of analysis, increased emphasis on supply chain transparency (13) to protect the lives of patients, and the availability of Product Quality Research Institute (PQRI)-defined options to finished excipient testing (14). The CoA Guide incorporates current best practices from industry and regulatory sources (15).

The IPEC Federation was established to better coordinate the work of IPEC-Americas, IPEC Europe, IPEC Japan, and IPEC China toward meeting the objectives of their member companies and the industry as a whole. Patient safety is a key driver of all IPEC guides. Because many pharmaceutical excipients now are manufactured, distributed, and used globally, the CoA Guide was bilaterally developed by IPEC–Americas and IPEC Europe. In addition, the CoA Guide will be provided to IPEC Japan and IPEC China for possible adoption and publication in their respective regions. Because the excipient trade is international, the CoA Guide will be an invaluable asset to the worldwide industry.

The CoA Guide was developed as a collaborative effort by excipient makers, distributors, and users. Members of the IPEC-Americas Excipient Qualification and the IPEC Europe Quality/Regulatory Affairs committees comprised the working group that developed the CoA Guide. IPEC member company issues were identified and addressed in the revision process, such as: absence of analytical method reference, computer software constraints, circumstances when the excipient manufacturer does not need to perform identification tests, legibility, absence of name and address of the original manufacturer, supply chain transparency, and use of terms other than expiration date or recommended re-evaluation date. In addition to IPEC member-company input, FDA has presented their thoughts on CoAs at various conferences and in meetings with IPEC–Americas, and FDA's comments were also addressed during the revision process.

International excipient GMP certification standards include requirements that are consistent with the CoA Guide. The NSF/IPEC 363 GMP for Pharmaceutical Excipients standard (currently under development) defines the minimum required CoA content. Also EXCiPACT *Certification Standards for Pharmaceutical Excipients: Good Manufacturing Practices/Good Distribution Practices* includes various CoA-related requirements.

The CoA Guide will be provided to the United States Pharmacopeia (USP) for their consideration in revising General Chapter <1080> Bulk Pharmaceutical Excipients—Certificate of Analysis, which is currently based on the CoA Guide 2000. Regulatory agencies and industry organizations such as Sindusfarma in Brazil and SaFyBi in Argentina also will be provided with the CoA Guide as part of an ongoing effort to harmonize excipient expectations worldwide.

Important changes

The CoA Guide details required content and recommended format and includes a model CoA, to be used as an example. It is recognized that existing computer software used to generate the CoA may pose constraints that limit the ability to achieve the recommended format. For this reason, the format of the model CoA provided in the CoA Guide is offered only as an example. It should not be erroneously construed that the recommended format must be followed.

Date format. Because the CoA Guide is of international applicability, an unambiguous date format is required so that dates (e.g., re-evaluation or expiration date) can be clearly communicated. One example of an unambiguous date format offered in the CoA Guide is to use alpha characters to designate the month and four digits to designate the year: DD MMM YYYY (e.g., 14 JUL 2013). This best practice ensures that excipients used in the manufacture of drug products meet specification requirements at time of use and that confusion does not lead to use of expired excipients.

Original manufacturer. The original manufacturer and manufacturing site should be identified if different from the supplier and supplier location. Specifically, the name and address should appear directly or by reference (i.e., using a code) on the CoA.

Regardless of whether or not a code appears on the CoA, the excipient user is responsible for knowing the name of the original manufacturer and the address of the original manufacturing site for every lot received. Where a code is used, the excipient supplier is responsible for defining the code to the excipient user, upon request. Such information may require a confidential disclosure agreement (16).

In addition to being a legal document and the basis of the excipient manufacturer's certification that the excipient will continue to meet the specification up to the re-evaluation or expiration date, the CoA is a crucial element of the overall supply-chain controls that excipient manufacturers, distributors, and finished drug manufacturers should have in place. To facilitate traceability to the excipient manufacturer, inclusion of the name of the original manufacturer and address of the original manufacturing site or an appropriate code on the CoA was emphasized in discussions that IPEC-Americas had with FDA.

Verification of authenticity. The excipient user should periodically verify the authenticity and validity of the CoA. This can be efficiently accomplished during a supplier audit or otherwise by sending the CoA to the issuer to verify that it is authentic. The frequency of such verification may be based on risk assessment, which takes into consideration the reliability of the excipient manufacturer and the supply chain involved.

The CoA should include the name and title of the person who authorized it. A computer generated CoA, where proper controls are in place at the excipient maker, provides an equivalent or better degree of assurance that the CoA is appropriately authorized than an original hand-signed document. There is no legal requirement to have a hand-signed CoA in most countries provided that appropriate controls are in place for an alternative computer-generated signature process.

If a distributor issues a CoA on their letterhead, their CoA should be traceable back to the original manufacturer's CoA. Also, the distributor's CoA should include the original manufacturer's name and location or code (if used).

PQRI defined options to finished excipient testing. The CoA Guide 2000 included provisions for "reduced frequency testing" by the excipient maker. Since the CoA Guide 2000 was issued, the Product Quality Research Institute (PQRI) Joint Position Paper on Pharmaceutical Testing and Control Strategies was published. As reported in this position paper:

"In a post-workshop meeting, FDA representatives stated that it considers the practice of skip-testing not to be compliant with cGMPs because for those lots that are not sampled and tested, there is a lack of assurance that the finished excipient material will meet all of its specifications. FDA believes that if an attribute for a finished raw material has required criteria, there must be some measurement or test of the material on each lot to ensure that the criteria are met" (14).

FDA stated in their response to the PQRI article and in subsequent discussions with industry that in-process testing can be used in place of finished excipient testing to determine compliance to a specified test parameter and to release an excipient product as meeting the appropriate specifications, provided the excipient manufacturer has clearly identified/documented the in-process "measurement" that directly relates to the specified test parameter and the in-process test clearly demonstrates that each batch of excipient would pass the requirement, if tested. This type of assurance can be obtained during an audit of the supplier. Without assurance of the correlation of in-process testing with a finished excipient test result from (e.g., supplier audits), the user is required to perform any test that is not performed by the excipient maker on each lot.

Based on FDA's comments, a user should no longer consider data from periodic (skip-lot) testing by the excipient manufacturer as sufficient to release the excipient for use in a drug product, regardless of the amount of historical data that may exist. This position is a paradigm shift for the pharmaceutical industry. Many companies use reduced testing programs and rely on their supplier's CoA data and, in the past, have accepted supplier statements that the specifications for a particular test were certified through the use of in-process or skip-lot testing. In addition, historically, pharmacopeias such as USP have allowed for this type of approach to be used by excipient manufacturers in their general notices and ICH Q6A has allowed for skip-lot testing of the drug product and drug substance. However, based on recent comments from FDA, they will not allow users to rely on in-process measurements to justify a specified test parameter without documented evidence (e.g., site audits) to demonstrate that appropriate procedures are in place to assure compliance. Although historically excipient users may not have established this level of documented evidence, but rather, may have simply relied on "un-justified/un-confirmed" data in their reduced testing programs, FDA made it clear during the PQRI discussions that this is now considered inappropriate (14). "According to FDA representatives, an appropriate determination to ensure that each lot conforms to appropriate specifications could involve some combination of the following approaches:

1. End-product testing
2. In-process testing
3. Continuous monitoring of an attribute with statistical process controls
4. Documented rationale that, based on the method of manufacture, the test attribute cannot be present and therefore the test is not applicable (e.g., residual solvents)" (14).

The CoA Guide refers to bullets 2–4 (above) as "other than finished excipient testing" and results derived from other than finished excipient testing should be clearly indicated in the CoA. For example, the test name can be footnoted to indicate the test result is obtained from other than finished excipient testing.

The CoA Guide also makes reference to ICH Q6A in this section, which allows for skip-lot testing of the drug product and drug substance. As mentioned above, FDA has additional expectations related to the use of supplier skip-lot testing results listed on a CoA for determining raw material compliance by pharmaceutical companies. FDA has stated that skip-lot testing by an excipient manufacturer by itself does not provide sufficient data for excipient users to justify reduced testing upon receipt and this lack of data was the basis of the PQRI discussions. Appropriate skip-lot testing can provide the basis, however, for an excipient manufacturer to certify compliance to a specification because the excipient manufacturer has significant process knowledge and understanding beyond what is available to the user. This is allowed for in the USP General Notices chapter, and there is no requirement for the excipient manufacturer to test each batch for all tests listed in their specifications when other controls can demonstrate ongoing compliance.

Verifying test results and measurements for specific parameters. Before releasing an excipient for use in the manufacture of a finished drug product, it is the excipient user's responsibility to ensure that a conforming test result was obtained for each specification parameter either by sampling and testing the finished excipient for each parameter, using qualified supplier test results from the CoA, or relying on "other than finished excipient testing" to support compliance to a particular parameter where qualified as noted above. The excipient CoA should identify these "other-than-finished excipient testing" results. Excipient makers should consider the impact on excipient users of any skip lot or "other-than-finished excipient testing" that is being used for product release at their site and inform excipient users accordingly.

Before accepting any test results from the CoA, the excipient user must qualify the excipient maker to ensure that the excipient is manufactured and tested in a manner consistent with applicable excipient GMP guidelines and excipient user requirements. The qualification should include a site audit of the excipient maker or supplier who provided the CoA by either the excipient user or a qualified third party to verify that the data provided on the CoA are generated using appropriate methods and are reliable. Periodic reassessment is also necessary to verify that the excipient maker remains qualified.

Whenever an excipient user relies on CoA data in lieu of incoming testing, it is suggested that an appropriate quality agreement be in place between the excipient maker and excipient user that clearly defines the responsibilities of each party. In such cases, the excipient maker serves, in essence, as a contract laboratory for the excipient user.

Analytical method reference. It is necessary that the excipient user know the analytical methods used by the excipient manufacturer to test each lot when CoA data are used for batch release. Analytical method references should appear on the CoA or be linked to a specification document so the analytical method used for each test is clearly communicated to the user. In the case where the analytical method is included on the linked specification instead of the CoA, the excipient user must be provided with the specification document.

Identification testing. *USP* General Notices 5.40 Identity states "A compendial test titled Identity or Identification is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers, and to establish whether it is the article named in *USP–NF*" (17). Furthermore, 21 *CFR* § 211.84(d)(1) states "At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be performed" (18). Similarly, for excipient users whose drug product is marketed in Europe, the EU legislation states, "The identity of a complete batch of starting materials can normally be ensured only if individual samples are taken from all the containers and an identity test performed on each sample (19)."

There has been confusion within the industry regarding reporting of identification tests on the CoA of excipient products. The IPEC CoA Guide clarifies that this reporting is not required when an excipient manufacturer has other control procedures in place that provide adequate assurance that their product will meet the identification test, if tested. In additon, the user must perform an identification test on every batch received regardless of whether the supplier has performed the identification test or not.

Summary

In summary, the CoA Guide is expected to be a crucial tool for manufacturers, distributors, and excipient users by providing clarity on additional regulatory and industry requirements related to supply chain transparency, authenticity of the CoA and testing requirements to name a few and by providing a suggested format that includes all necessary information.

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Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect that of their employers.

Ann Newman, PhD, is a principal consultant for Patheon.

Measuring API Particle Size Distribution

Visual mapping can provide a particle-size distribution estimate.

Q. Is there a clever way to directly measure drug/API particle size distribution in a tablet blend/granulation, assuming API has very low aqueous solubility and the excipients are in a mixed (either water-soluble or insoluble) state?

A. One method that I have used to directly estimate/measure the particle size of API particles in tablets, which would also work for blends and granulations, is mapping. By picking a peak unique to the API, a visual distribution of the API can be obtained. In order to get a particle size distribution, you would need to extend the analysis by counting the dimensions for a relevant number of particles. Many times a simple visual assessment is enough to easily see differences based on parameters such as starting material or processing.

A visual map is obtained that can be used to estimate the particle size of the API visually.

Mapping can be performed using a variety of techniques including infrared (IR), Raman, energy dispersive x-ray (EDX), and even X-ray powder diffraction (XRPD). EDX analysis, performed in a scanning electron microscope (SEM), can be used for API molecules that contain elements amenable to EDX (usually above carbon in the periodic table). In my project, the API contained a chloride ion that was not present in any of the excipients. By mapping the presence of the chloride, the API particle size present in two tablets were directly compared and related to dissolution data to help explain a slower dissolution rate. For spectral mapping, an API peak is needed that does not overlap with the excipients in the formulation. The API peak is then used to map the presence of the API in the sample. A visual map is obtained that can be used to estimate the particle size of the API visually or an additional step of measuring the size of relevant areas can be performed. The limitation will be the magnification of the microscope used; smaller particles will require higher magnifications. Resolution of the technique will also play a role and can be controlled by the instrument source and the experimental parameters. Higher resolution will require smaller analysis steps and longer scan times. These factors will need to be considered when you set up your experiment to determine the amount of time and effort that is needed for the information you want to obtain.

What would you do differently? Email your thoughts to Managing Editor Susan Haigney at **shaigney@advanstar.com** and we may post them on **PharmTech.com**.

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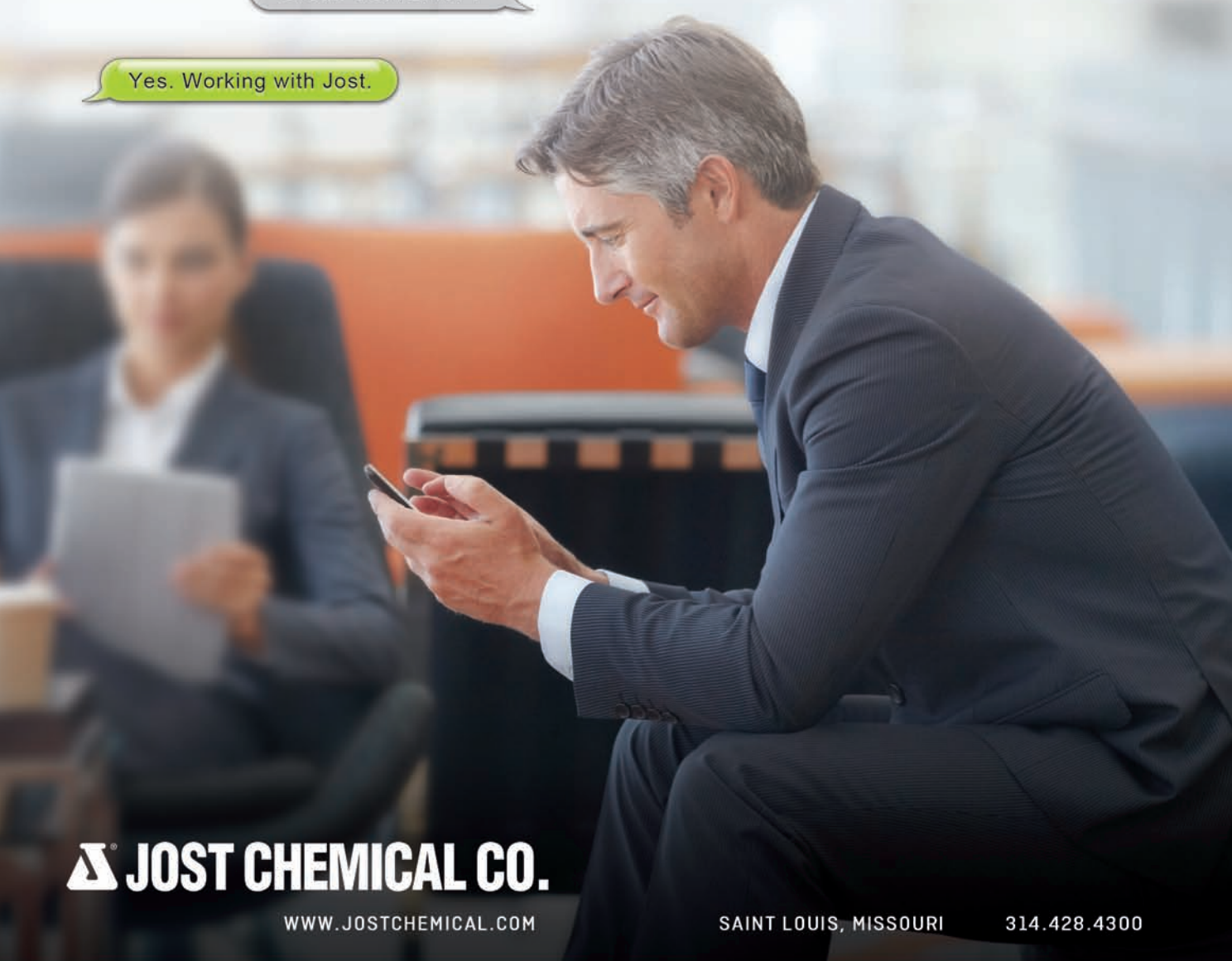

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EMERGING MARKET REPORT

Report from: Brazil

Hellen Berger

Brazil's major vaccine producer innovates with stem-cell research.

In 1898, an outbreak of Bubonic plague struck the port of Santos in São Paulo, Brazil. A year later, a local bacteriological institute set up a unit to produce anti-plague serum in a government-owned farm known as Butantan, which was renamed the Butantan Serumtherapy Institute in 1901.

The institute started gaining global recognition as it ventured into research on animal venom, which consequently led to the production of anti-venom. In 1915, the institute was renamed Butantan Institute. Known as Butantan, the institute currently conducts technical and scientific activities in two major areas—the production of serum and biomedical research.

The institute claims to be Latin America's biggest vaccine producer, with an output of more than 300 million doses every year. Today, Butantan is considered a major contributor to Brazil's public health, having approximately 1700 staff members, including 180 scientific researchers specializing in innovation.

Innovation using Brazilian technology

"I believe Butantan Institute is an important partner to [Brazil's pharma] companies as 80% of all vaccines used in Brazil are produced by this institute," says Irina Kerkis, director of the genetics laboratory at Butantan Institute. Despite its struggles in a globally competitive market, the institute reaches for innovation while balancing research and production according to its researchers.

In its search for local and global recognition, Butantan has developed major research capabilities at its genetics laboratory, including the expertise to retrieve stem cells from milk teeth. Nelson Foresto Lizier, a scientific researcher working at Butantan's genetics laboratory, says that this project is vital given that stem cells have the ability to generate almost any human cell. The study, which is considered the first of its kind in Brazil, is being developed with "100% Brazilian technology" according to Lizier.

The development of the technology started in 2004. It was initially privately funded; however, six years later, investment from major public agencies began pouring in according to Kerkis.

Implications for the pharmaceutical sector

Private pharmaceutical companies in Brazil acknowledge the importance of stem-cell research. "Butantan and the national pharmaceutical industry are major partners and the institute is willing to develop research studies together with the private sector," says Henrique Uchió Tada, executive technical director for the National Pharmaceutical Laboratories Association (Alanac).

According to Tada, the various potential benefits and applications of the stem-cell project include, among others, treatments for diabetes, heart illnesses, liver problems, multiple sclerosis, brain lesions, Parkinson disease, inflammatory diseases, and the recovery of human skin and organs. "However, the development of related pharma products is still a little far away for the national pharmaceutical industry," he adds. Tada explains that stem-cell studies conducted by national pharmaceutical laboratories focus on a type of treatment that is not considered traditional. He says that treatment is obtained through the retrieval of stem cells from the individual's body and not through a synthetic drug applied for treating an entire population with the exact same illness or disease.

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Several bioethics experts in Brazil believe that there may be a gap between the pharmaceutical industry and stem-cell treatments. The future might not require the use of drugs as we know them, they say. For example, patients would be able to use their own cells to cure diseases, and as a result, the pharmaceutical industry would be affected because of profit loss from the steep drop in sales. Tada, however, believes that pharmaceutical firms could benefit from stem-cell advances if they develop a method that makes use of stem cells in treatment procedures.

According to both Kerkis and Lizier, the pharmaceutical industry has shown great interest in stem-cell research because of its potential as "biotools" for developing and testing new products. "The development of new drugs through the study of stem cells could become a reality by conjoining findings from pharmacology and cellular biology studies as the variety of substances produced by cultured stem cells could open new doors for pharmacology in general," says Kerkis, whose statement was supported by Lizier.

Butantan's stem-cell research

Embryonic stem cells, obtained by a special technique developed by Butantan researchers, are already being tested in humans. According to the institute, results from these clinical studies, which involve reconstruction of the tissue that covers the human eye cornea for example, are expected to be reported during the second half of 2013.

Butantan's biggest finding is that, through the method developed, it is possible to obtain sufficient quantities of cells to be applied in humans. According to Lizier, one of the advantages of working with stem cells from milk teeth is that these teeth are biological materials that are generally discarded and children have an average of 20 milk teeth that are changed during their lifetime. Moreover, the extraction of the internal material from the teeth is simple and not as painful when compared with other techniques.

With the method developed at Butantan, it is possible to obtain cells that are considered immature compared with other populations of adult stem cells found in other tissues. According to Lizier, the technique uses cells that are similar to embryonic cells, but without the bioethics issues involved or the possibilities of inducing tumor growth during treatments. Using Butantan's technology, researchers can retrieve approximately 100 billion cells from a small fragment of dental pulp. "The figure is big enough for treating up to 100 patients," says Lizier.

Butantan has scientific proof that stem cells from milk teeth could play an important and safe role in treatments involving bone, cartilage, muscle, and neural tissue regeneration as well as in therapies for immune and metabolic disorders and dentistry. As the research develops, other applications of the institute's technology could prove useful in the near future. **PT**

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

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Advances in PAT for Parenteral Drug Manufacturing

Patricia Van Arnum

Applying quality-by-design and process analytical technology facilitates process understanding and control of various operations in lyophilization.

When FDA announced in 2002 a new initiative, *Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century*, and later issued its report, *Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach*, in 2004, it began an effort to enhance product quality and modernize pharmaceutical manufacturing through a science- and risk-based approach under quality-by-design (QbD) principles (1). That effort was further encouraged by the issuance of guidance on process analytical technology (PAT) in 2004 to facilitate new technologies that would enhance process understanding and assist in identifying and controlling critical points in a process (2). These technologies include: appropriate measurement devices, which can be placed at-, in-, or on-line; statistical and information technology tools; and a scientific-systems approach for data analysis to control processes to ensure production of in-process materials and final products of desired quality (1–4). Lyophilization is one specific application of QbD and PAT in parenteral drug manufacturing, and a review of recent literature shows several developments in this field.

Evaluating the technology

In applying QbD to the lyophilization process, the first task is to define the parameters that have the potential to affect process performance and product-quality attributes (5). Key points include the freeze-drying process operating parameters, formulation parameters, equipment, and component preparation and devices (5). PAT may be applied through sensors at various stages in freeze-drying, which may include using temperature sensors, pressure-rise analysis, manometric temperature measurements, calorimetry, microscopy, and spectroscopic techniques, such as near-infrared (NIR), Raman, and infrared spectroscopy (6).

Assessing the tools

An established approach for PAT in lyophilization is offered by SP Scientific's SMART freeze-dryer technology, which is used to optimize the freeze-drying cycle. The SMART technology was developed by the University of Connecticut and Purdue University through the Center for Pharmaceutical Processing Research and licensed to SP Scientific. The technology relies on the use of manometric temperature measurement, which calculates the product temperature at the sublimation interface without having to place thermocouples or other temperature sensors in product vials (7). The SMART freeze-dryer technology is used on SP Scientific's Lyostar 3 development freezer. The SMART technology uses information, such as the number of vials, fill volume, fill weight, freeze-dryer chamber volume, and critical formulation temperature to optimize a cycle (8). It contributes to several key points in lyophilization: selects an optimum freezing cycle based on whether the formulation is crystalline or amorphous; selects the optimum chamber pressure; determines the target temperature of the product; and adjusts the shelf drying during primary drying to keep the product at a predetermined target temperature (8).

SP Scientific has partnered with the industrial-gas company Praxair for another PAT-based tool for lyophilization, Praxair's ControLyo Nucleation on Demand Technology, used to control the nucleation of the product solution in the freeze dryer. The companies first partnered in 2010, which gave SP the exclusive, global rights to commercialize the technology on development lyophilzers. In 2012, the companies expanded their collaboration to allow SP Scientific to equip its clinical, pilot, and production dryers with the ControLyo Technology and to transfer the technology to allow SP to retrofit existing pilot and production units.

IQ Mobil Solutions, based in Holzkirchen, Germany, offers wireless and battery-free temperature sensors (Temperature Remote Interrogation

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System, TEMPRIS) as a PAT tool for lyophilization. In a recent study, the TEMPRIS system was assessed for measurement accuracy, capability of accurate endpoint detection, and effect of positioning by using product runs with sucrose, mannitol and trehalose (9). Data were compared to measurements with 36-gauge thermocouples and to noninvasive temperature measurement from manometric temperature measurements. The results showed that the TEMPRIS temperature profiles agreed with thermocouple data when sensors were placed center bottom in a vial. In addition, TEMPRIS sensors revealed reliable temperature profiles and endpoint indications relative to thermocouple data when vials in the edge position were monitored (9).

A recent study evaluated an optical-fiber system as a process monitoring tool.

Researchers at Ghent University in Belgium used Raman and NIR spectroscopy as PAT tools in a freeze-drying process (10). For the study, Raman and NIR probes were built in the freeze-dryer chamber to allow simultaneous process monitoring of a 5% (w/v) mannitol solution. Raman and NIR spectra were continuously collected during freeze-drying and analyzed using principal component analysis and multivariate curve resolution (10). Raman spectroscopy provided data about the mannitol solid state, the endpoint of freezing, and several physical and chemical conditions (e.g., onset of ice nucleation and onset of mannitol crystallisation). NIR spectroscopy monitored key points in drying, the endpoint of ice sublimation, and the release of hydrate water during storage (10). A later study further examined the use of in-line spectroscopic process analyzers (Raman, NIR, and plasma emission spectroscopy) (11).

Another recent study examined the use of tunable diode laser absorption spectroscopy (TDLAS) for monitoring secondary drying in laboratory-scale freeze-drying with the purpose of targeting intermediate moisture contents in the product (12). An earlier study examined TDLAS to determine the average product temperature in primary drying (13).

Other approaches

Researchers recently implemented and evaluated an optical-fiber system as a process-monitoring tool during lyophilization. The study recorded temperature profiles of mannitol, sucrose, and trehalose using various prototypes of optical fiber sensors (OFSs) (14). The data were compared to data obtained with conventional thermocouples or Pirani/capacitance manometry with respect to the endpoint of primary drying. The researchers reported that the data obtained with the OFS in contact with product were in

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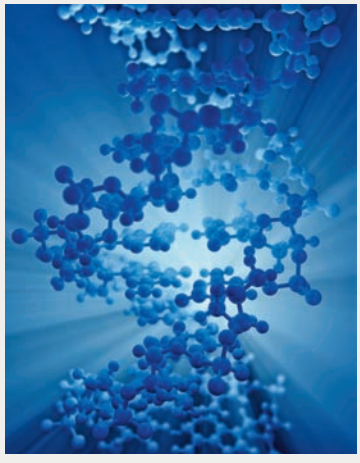

As biopharmaceutical/pharmaceutical companies increase their development of biologic-based drugs, companies providing analytical instrumentation and laboratory testing goods and services are, in turn, offering improved tools for biologic characterization, biomanufacturing, and related testing.

In December 2012, Sartorius Stedim Biotech (SSB) expanded its process analytical technology software capabilities by partnering with Umetrics, a provider of multivariate technology, including software for design of experiments (DoE) and multivariate data analysis (MVA). Under the pact, SSB assumes global marketing and distribution of the Umetrics portfolio for the pharmaceutical and biopharmaceutical industries and will integrate Umetrics software programs as private-label products into its own bioprocess portfolio and market these as stand-alone solutions under a dual branding arrangement. The major areas for these software systems are critical process steps, such as cell-culture processes or specific purification steps. MVA enables process parameters to be added in batch trajectories, and DoE software permits these critical process parameters to be identified and quantified.

In January 2013, Waters expanded its biopharmaceutical platform solutions with UNIFI, new ACQUITY ultra-performance liquid chromatography (UPLC) CSH130 C18 and XSelect HPLC CSH130 C18 columns for peptide mapping, and three GlycoWorks kits for glycan labeling and sample preparation. These products further progress routine biotherapeutic analysis, particularly for glycoproteins that require analysis of glycan modifications as well as protein- and peptide-level structural analysis. The biopharmaceutical platform solution brings together UPLC/mass spectrometry (MS) characterization technology with the UNIFI Scientific Information System that was first developed for intact protein mass analysis, peptide mapping, and supporting general bioseparations. The expansion supports a mix of quadrupole time-of-flight (Q-TOF) MS and optical-detection instruments within a networked laboratory workgroup. The newly released Glycan application workflow expands the platform's capabilities to support routine assignment and profiling of released glycans using fluorescence detection. The combination of high-performance UPLC HILIC (hydrophilic interaction liquid chromatography) separations, the company's calibration standards and reagents, and access to Ireland's National Institute for Bioprocessing Research and Training (NIBRT)/Waters' GlycoBase 3+ UPLC glycan unit reference database enables glycan assignments, quantification, and profiling. Developed by Prof. Pauline Rudd's research team at NIBRT, the GlycoBase 3+ database is a repository of glycan chromatographic retention data, expressed in glucose calibration units, and which encompasses sets of glycan structures associated with biotherapeutic glycoproteins.

Also in January 2013, PerkinElmer launched the JANUS BioTx Pro automated workstation for improved process development of proteins. The workstation is designed for high-throughput, small-scale protein purification (of µg to mg proteins) and accommodates multiple chromatography modes (column, tip and batch). It supports commercially available plate and column-based screening tools, such as GE PreDictor plates, PhyNexus PhyTip columns, and Atoll columns. Applications for the workstation include resin-binding studies and conditions screening.

In May 2012, Shimazdu launched an improved Accurate Glycan Analyzer 2 (AGA2), which provides a glycan database and the company's AXIMA Resonance, a MALDI (matrix-assisted laser desorption/ionization)–QIT (quadrupole ion trap)–TOF (time of flight) mass spectrometer. The AXIMA Resonance is coupled to a database containing glycan structural information generated from actual MS^n spectra to select precursor peaks up to MS^4. The resulting spectra are interpreted to return the most likely glycan structure. The AGA2 was created from biosynthesized glycans and contains well-defined and characterized, biologically relevant, glycans. It also uses common fluorescence-labeling schemes, including 2-aminopyridine, 2-aminobenzoic acid and 2-aminobenzamide, and other types of fluorescence labeling.

In February 2013, Thermo Fisher Scientific expanded its high-content analysis portfolio with three new solutions in cell biology: the Thermo Scientific ArrayScan XTI High Content Analysis (HCA) Reader, Thermo Scientific CellInsight NXT High Content Screening (HCS) Platform, and the Thermo Scientific X1 upgrade for current ArrayScan VTI customers. Each of these products features a large-format, sensitive CCD (charged-coupled device) camera, the Thermo Scientific HCS Studio software suite, and greater processing capabilities. The Thermo Scientific X1 CCD camera, used for high-content analysis, offers improved sensitivity, increased resolution, and a large field of view.

Thermo Fisher Scientific also introduced the Thermo Scientific Dionex GlycanPac AXH-1 HPLC column, which is designed for simultaneous separation of biologically important glycans based on charge, size, and polarity. The column is designed to separate both labeled and native glycans based on the availability of samples. Native glycan separation allows researchers to eliminate the fluorescent labeling step and increase throughput.

In 2012, Agilent Technologies partnered with Spain's Center for Omic Sciences in mass spectrometry and NMR (nuclear magnetic resonance)-based metabolomics and automation for use in integrated systems biology. The Center for Omic Sciences (COS) was established by the Rovira i Virgili University in collaboration with Spain's Technological Center of Nutrition and Health. COS opened in September 2012 and is equipped with instrumentation from Agilent. The COS is a center of excellence where Agilent will demonstrate integrated biology workflows in genomics, proteomics, transcriptomics, lipidomics, and metabolomics.

In November 2012, Bruker launched METALJET, a bright microfocus X-ray source for structural biology applications. METALJET is a source option for D8 VENTURET protein crystallography systems and for NANOSTAR Small Angle X-ray Scattering (SAXS) systems. The METALJET source for Bruker structural biology systems was developed in collaboration with Excillum AB and Incoatec GmbH for use in protein crystallography and SAXS applications.

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good agreement with data obtained by thermocouples or Pirani/capacitance manometry. The OFSs showed higher sensitivity, faster response, and better resolution compared to thermocouples (14). Another study examined the use of a soft sensor for in-line monitoring of the primary drying step of a freeze-drying process in vials (15).

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The Lifecycle Change of Process Validation and Analytical Testing

Susan Haigney

PharmTech spoke with industry experts about the effect FDA's 2011 process validation guidance has had on industry.

In the two years since the publication of FDA's final guidance, *Process Validation: General Principles and Practices* (1), how has this new lifecycle approach affected the way the industry performs validation? *Pharmaceutical Technology* spoke with Hal Baseman, COO and principal at ValSource LLC and co-leader of the Parenteral Drug Association Process Validation Interest Group; Paul Smith, EMEAI laboratory compliance product specialist at Agilent; and Ian Jones, CEO, and Luke Kiernan, technical services director, of Innopharma Labs in Dublin, about the impact FDA's process validation guidance has had on analytical testing and validation.

Continuous process verification

PharmTech: What are the key elements of continuous process verification?

Jones (Innopharma Labs): A manufacturer can only truly understand their process and successfully demonstrate continued process verification through the implementation of process analytical testing (PAT) technologies to support the monitoring and control of product critical to quality attributes. I think material understanding throughout the manufacturing process from the product development phase onwards will not only support a robust commercial manufacturing process but can also reduce the burden of scale-up and technology transfer, thereby supporting product-divestment initiatives. The implementation of the new FDA guidelines on process validation will not only meet the expectations of the regulator but can also ensure the success of business demands such as lean scale-up, commercial manufacture, and technology transfer.

Smith (Agilent): Continued process verification requires an ongoing collection of data and evaluation of the performance of the process using the data collected. Historically, organizations tended to limit the "dimensionality" of the process data they gathered and monitored. Typically, this included a smaller number of discrete pieces of data, significantly less than that generated by continuous process monitoring as part of the lifecycle approach.

The identification, training, and use of appropriate statistical tools in the lifecycle approach are essential to the success. To detect a small change in a process or a process drift, the underlying variability of the process when operating 'normally' must be understood. Automated algorithms can fail. Typically, this can occur when there is some new source of variation/change in the relationship between the data that are being monitored that impact the underlying assumptions in the automated algorithms. Reliance on complex and sophisticated sales algorithms in the stock market is an example of this type of error. On the other hand, humans can make simple errors. Therefore, finding a balance between relying on semi-automated statistical tools and human monitoring is potentially one of the key elements to success.

Applying PAT

PharmTech: How may a given manufacturing process (including equipment design and operation) and analytical testing need to be modified to accommodate this lifecycle approach?

Baseman (ValSource): PAT can be a key element of continuous process verification. In-line, continuous monitoring, and control systems, such as those associated with PAT, are helpful in maintaining and assuring process control. Assurance of process control can be obtained by observation, inspection, or evaluation of process parameters and product attributes. Where complete observation is not possible, companies need to predict process outcome. Validation is the prediction of outcomes that cannot be fully observed, based on information we can observe. The more that [we] can observe, the more accurate the prediction.

In-line monitoring and control systems allow for more process observation, as well as better control of the process, further assuring process performance. In addition, they provide effective knowledge-management tools, providing information that can be utilized for future validation activities.

Jones (Innopharma Labs): I think PAT technologies can support all aspects of the product lifecycle—process development, scale-up, commercial manufacture, and technology transfer. You can't successfully conduct these lifecycle activities without intimate process understanding. This is only achieved on a batch-to-batch basis through real-time in-line PAT. Where this is not possible, on-line or at-line are also a necessary compromise.

Smith (Agilent): The lifecycle approach represents a different way of designing, building, and monitoring manufacturing processes. Within those processes, many of the key process stages associated with manufacturing have not changed significantly: blending, distillation, drying, and crystallization, for example. Many early PAT applications have been an adoption of laboratory instrumentation to process operation. A key challenge of this early PAT adoption, such as near infrared has been the limitations of access points in the manufacturing equipment, where a

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probe, signal, or at-line sampling point can be implemented. Cutting a hole in a glass-lined vessel is simply not an option. Therefore, the use of PAT must be considered at the process-design stage.

Generally, the simpler the technology and an understanding of the underlying relationship between what the PAT device is actually measuring and how the results will be used to monitor/adjust the process, potentially, the more robust the process should be. Therefore, simple PAT applications designed to support these discrete process stages are required. All PAT applications need to have some assessment of 'is it working correctly' built in, as well as appropriate means of efficiently performing 'instrumental activity' such as maintenance and/or calibration.

Lifecycle versus traditional validation

PharmTech: How does a lifecycle approach to process validation that employs risk-based decision-making throughout that lifecycle differ from traditional validation protocol and practice?

Baseman (ValSource): The principles of any effective process validation approach should consider risk to product quality and quality risk management tools in validation-related decisions; glean information from process design studies to identify process variables; develop control strategies and use sound scientific rational to test the effectiveness of those strategies during the qualification of the process; and monitor variability of commercial manufacturing batches to support maintenance of the validated state and look for ways to improve and optimize the process.

Jones (Innopharma Labs): There is a significant difference. With additional material understanding and a greater development focus, there is tremendous potential to reduce the process qualification burden and enhance process robustness throughout the lifecycle of the commercial product. Through the adoption of a lifecycle approach, there is the opportunity to not only continuously verify your process but also to continuously improve your process through greater automation, operator understanding, and PAT-instrument implementation. If adopted correctly, this guideline is good news for the regulator, the pharmaceutical manufacturer, and the patient because we will see more robust, reliable, and better value products brought to market.

Smith (Agilent): The original 1987 FDA process validation document was implemented at a time where compliance thinking was quite different to what it is today. At the time, the emphasis was more on 'Locking down the process' and generating documented evidence. In other words, the process was fixed and the emphasis was on the qualification documentation.

A key industry interpretation of the 1987 guidelines was the implementation of three validation batches during the process validation. This 'requirement' was not expressly stated in the 1987 guide, but rapidly became the 'industry norm.' A process could be considered validated if the results of the three validation batches passed specification, and the suite of qualification documents produced were well written. Ultimately, this potentially contributed towards a mindset that validation could be bolted on to a process while the underling science and variability of the process might not have been well understood and problems were often encountered when processes were transferred between organizations. The 2011 guidance aligns process validation with product lifecycle principles that are now part of current regulatory thinking and principles.

Challenges

PharmTech: What are the key challenges in implementing a lifecycle approach to process validation compared to the traditional process validation?

Baseman (ValSource): Companies used to running 'three batches' to qualify processes will need qualified resources to develop scientifically sound process validation plans, collect and analyze process performance metrics, and answer the question: how does what you do to validate the process, and provide assurance that the process is adequately controlled?

Companies may not yet have the systems in place to identify and transfer information from process design related groups to the people responsible for planning and conducting the process qualification studies. Also, companies may be concerned that using prior knowledge from previously validated processes to support the validation of new processes will expose those older processes to regulatory scrutiny.

Additionally, companies, which use CMOs and other outsourcing organizations, may not yet have the systems in place to adequately capture and transfer information needed to support the lifecycle approach to and from those organizations. And lastly, companies uncovering opportunities for process improvement during Stage 3, Continued Process Verification may be concerned that submitting changes to those processes will risk further regulatory scrutiny to already 'validated' processes.

Kiernan (Innopharma Labs): The guideline requirements are that the manufacturer must judge whether it has gained sufficient process understanding to justify commercial distribution of the product. The initial challenge for the manufacturer is to understand what sufficient process understanding 'looks like'. In Stage I, what level of design-of-experiment work is required? In Stage II, How many validation batches are sufficient (is three still the magic number)? And in Stage III, how much additional testing/monitoring is required? A greater knowledge of statistics and statistical control is now required by the manufacturer compared to when the traditional approach to process validation was in place.

Other challenges relate to legacy products that now fall into Stage III of the lifecycle. The same level of data-driven process understanding may not be available for these products as for new products. The challenge for manufacturers is to meet the requirements of the guidelines in a cost effective manner, for legacy products.

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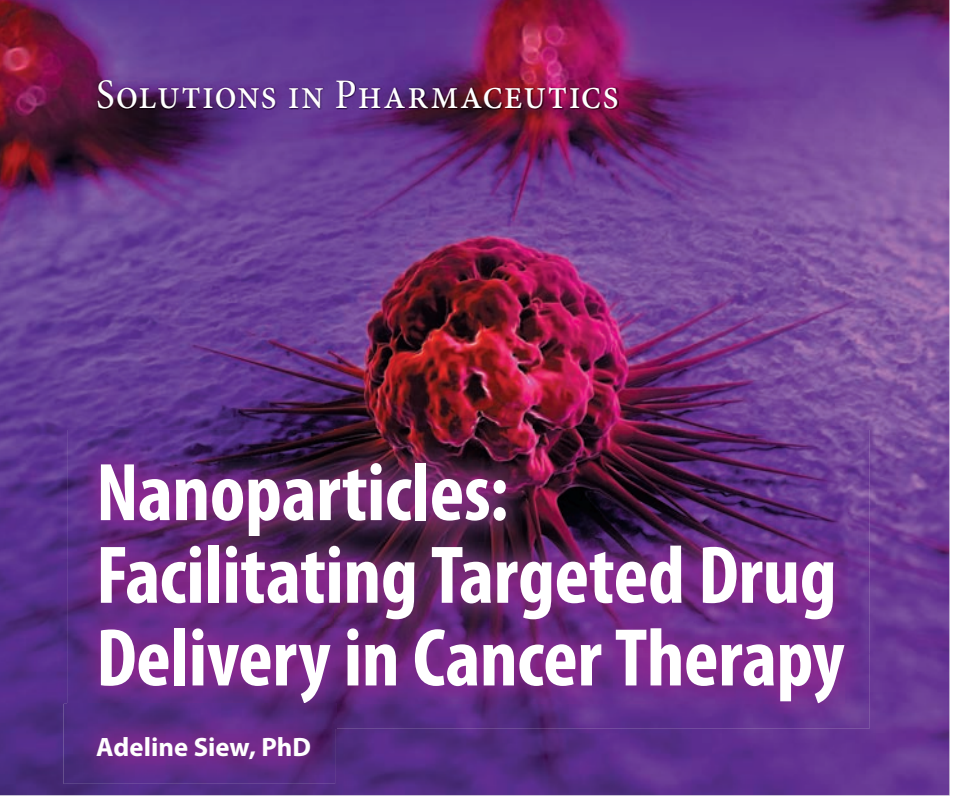

Nanoparticles: Facilitating Targeted Drug Delivery in Cancer Therapy

Adeline Siew, PhD

***PharmTech* spoke to Robert Langer, professor at the Massachusetts Institute of Technology and founder of BIND Biosciences; Stephen Zale, vice-president of development at BIND Biosciences; and Yanli Zhao, assistant professor and national research foundation fellow at Nanyang Technological University, Singapore, about engineering nanoparticles with optimal properties for use in cancer therapies.**

Nanoparticles have significantly changed the scientific landscape of disease treatment, prevention, and diagnosis, generating a new wave of nanoscale drug-delivery strategies. From solubility/bioavailability enhancement (1, 2) and targeted drug delivery (3, 4) to controlled/sustained release (5, 6) and protection of labile molecules (e.g., proteins, peptides, and DNA) from enzymatic degradation (7, 8), these structures can be manufactured, controlled, and manipulated to take on novel properties and functions that have opened new doors in the biomedical arena.

While nanoparticles may vary in size ranging from 10 nm to 1000 nm, nanomedicines are typically less than 200 nm (9). Nanoparticles made from natural or synthetic polymers have gained popularity because of their stability and ease of surface modification. They can be engineered to achieve controlled drug release as well as specific localization at disease sites by modification of the polymer characteristics and surface chemistry. For example, it has been well established that nanoparticles accumulate preferentially at tumor and inflammatory sites due to the enhanced permeability and retention effect (EPR) of the vasculature (9–11). At the target site, the biodegrable polymeric nanoparticles can act as a local drug depot that provides continuous release of the encapsulated therapeutic agent.

These advantages offered by nanoparticles for targeted drug delivery are a result of their small size and the use of biodegradable materials. The small size enables the nanoparticles to overcome biological barriers (e.g., gastrointestinal epithelium, tumor vasculatures, and endothelium of inflammatory sites) and achieve cellular uptake while the use of biodegradable materials allows for sustained drug release at the target site (9–11).

Advances in the development of nanoparticles have seen these systems being translated into clinically useful medicines, particularly in the treatment of cancer. Examples of nanoparticle-based medicines approved by FDA and EMA as cancer therapies include Doxil and Myocet (liposomal formulations of doxorubicin), DepoCyt (liposomal cytarabine), DaunoXome (liposomal daunorubicin), Abraxane (an albumin-bound formulation of paclitaxel), and Genexol-PM (a polymeric-micelle formulation of paclitaxel).

Nanomedicines in clinical evaluation

A number of nanoparticle-based formulations are in clinical development as potential treatments for cancer. NanoCarrier's nanoplatin (NC-6004), which consists of cisplatin incorporated into micellar nanoparticles composed of polyethylene glycol (PEG) and polyglutamic acid block copolymers, is undergoing Phase II evaluation in patients with advanced or metastatic pancreatic cancer (12). Preclinical results showed that nanoplatin accumulated in cancer cells and had significantly lower nephrotoxicity and neurotoxicity (13). In a Phase I study conducted in the UK, the formulation was well tolerated in patients with solid tumors, providing sustained and prolonged release with minimal nephrotoxicity and no significant myelosuppression, ototoxicity, emesis, or neurotoxicity (14).

Cerulean's CRLX101 consists of the topoisomerase-1 inhibitor, camptothecin, covalently conjugated to a PEG-β-cyclodextrin copolymer that self assembles into nanoparticles of approximately 30 nm in diameter (15). Unlike camptothecin, these nanoparticles have a long circulation half-life, enabling them to accumulate in the tumors. Following uptake of CRLX101 into tumor cells, the active camptothecin is gradually released from the nanoparticles, providing a sustained concentration of the drug in tumors. It has been observed that this sustained concentration of camptothecin at the tumor site results in the inhibition of HIF-1 alpha, a hypoxia-induced transcription factor known to regulate cancer cell survival, metastasis and drug resistance. Studies have demonstrated that CRLX101 nanoparticles augment camptothecin efficacy by facilitating localization and retention at the target tissue, increasing intracellular drug deposition, providing a sustained supply of active camptothecin, and prolonging drug activity at the target site (16). CRLX101 is in Phase II evaluation for the treatment of various tumor types (15).

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Nippon Kayaku's NK105, a nanoparticle-based formulation of paclitaxel incorporated into block copolymers of PEG-polyaspartate, was developed to enhance the antitumor activity of paclitaxel while reducing adverse effects such as neurotoxicity, myelosuppression, and allergic reactions (17). NK105 is currently in Phase III development and studies are being conducted to investigate if NK105 can improve progression-free survival in patients with metastatic or recurrent breast cancer.

Other examples of molecular-targeted nanoparticle-based cancer therapeutics in clinical development include BIND Biosciences' BIND-014 (Phase I), Calando's CALAA-01 (Phase I), Mebiopharm's MBP-426 (Phase I/II), and SynerGene's SGT53-01 (Phase I).

Pharmaceutical Technology spoke to Robert Langer, professor at the Massachusetts Institute of Technology (MIT) and founder of BIND Biosciences; Stephen Zale, vice-president of development at BIND Biosciences; and Yanli Zhao, assistant professor and national research foundation fellow at Nanyang Technological University (NTU), Singapore, about engineering nanoparticles with optimal properties for use as cancer therapies.

Building in optimal properties

PharmTech: What are the key considerations when designing nanoparticles for the delivery of cancer therapeutics? How do you engineer these nanoparticles to achieve targeted delivery?

Zale (BIND Biosciences): This is a complicated question because the effects of many characteristics on how nanoparticles behave in the human body are interdependent on one another. Broadly speaking though, for nanoparticles to be effective, they must be able to circulate in the bloodstream, extravasate into diseased tissues, and release their therapeutic payload at a rate that provides high concentrations at the target site.

We use particles based on copolymers of polylactic acid (PLA) or copolylactic/glycolic acid (PLGA) and PEG, and attach targeting ligands to the end of the PEG chain. We have developed a particle-manufacturing process that encapsulates the drug payload in the PLA/PLGA core of the particle and orients the PEG and the targeting ligand toward the surface of the particle. PEG gives the particle a water-like corona, which disguises the particle from the systems in the body that would otherwise remove them from the bloodstream within minutes after administration. As a result, our nanoparticles display circulation half-lives of nearly 24 hours and are able to concentrate drugs in tumors at levels typically 10 times greater than when the same dose is given as a solution.

Passive targeting is often not enough to eradicate the side effects of cytotoxic drugs.—Zhao

Langer (MIT and BIND Biosciences): We have used a broad range of targeting ligands, including antibodies, antibody fragments, aptamers, peptides, and small molecules. We have studied a range of targets including, for example, well-established and clinically validated tumor targets such as the prostate-specific membrane antigen (PSMA) and human epidermal growth factor receptor 2 (HER2), and have discovered our own targets and ligands in areas such as cardiovascular disease. At BIND, rapid clinical translation is important, and therefore, the focus is on validated targets in areas of unmet clinical need such as cancer, and primarily using peptide and small-molecule ligands for targeting.

There are many antigens or receptors expressed by cancer cells or the surrounding tissue that can be targeted by peptide and small-molecule ligands, which are inherently more stable and less complex than macromolecular ligands such as antibodies and aptamers. For examle, while our initial studies employed an aptamer that targets PSMA, BIND switched to a PSMA-binding small molecule in BIND-014, which enabled them to quickly move into clinical development with a simple, pharmaceutically stable, and well-characterized targeted particle. This PSMA-targeted particle can be manufactured reproducibly at large scale and has been shown to be nontoxic in animal studies.

Zhao (NTU): Nanoparticles tend to aggregate as a result of their large surface-to-volume ratio in biological media. When nanoparticles agglomerate, they not only lose their intended functionality, but are quickly recognized and effectively removed by the mononuclear phagocytic cells in the reticuloendothelial system (RES) of the liver and spleen. This sequestration is often increased by the surface coating of nanoparticles with a corona of proteins that leads to opsonization and enhanced phagocytosis by the RES.

A strategy to maintain good dispersion of drug-loaded nanoparticles in biological media is by surface modifications with PEG polymers. PEG has been known to prevent protein adsorption (opsonization) on the nanoparticle surfaces, enhance circulation time, reduce nonspecific RES uptake, and facilitate preferential accumulation at tumor sites through the EPR effect. Passive targeting in itself, however, is often not enough to eradicate the side effects of cytotoxic drugs and divert the anticancer therapy away from healthy cells to selectively target cancer cells.

To further enhance the targeting ability of drug-loaded nanoparticles, these systems must also be coupled with targeting agents that can actively bind to over-expressed antigens or receptors on the surface of cancer cells. Drug-loaded nanoparticles can be engineered to recognize and bind to cancer cells through ligand-receptor interactions and the bound nanoparticles are internalized before the loaded drug is released inside the cells. Finally, there is another concern that these drug-delivery systems should release the loaded drug rapidly upon accumulating at tumor sites and after being taken up by cancer cells.

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Designing nanoparticles for selective targeting

PharmTech: Could you describe your research on nanoparticles as targeted drug delivery systems in the treatment of cancer?

Langer (MIT and BIND Biosciences): The idea of employing targeted nanoparticles to bring cancer drugs to the site of disease and increase their safety and effectiveness has been around for several decades, but until recently the solution has been elusive. A major obstacle has been the inability to achieve the optimal interplay of particle characteristics that confer targeting of diseased cells, evasion of particle clearance mechanisms, and controlled release of the encapsulated drug payload.

In the mid 2000s, Omid Farokhzad at Harvard Medical School and I developed a new approach for targeting of drug-loaded polymeric nanoparticles to disease sites, including cancer cells and diseased vasculature. The technology is based on a novel self-assembly process which allows formation of nanoparticle libraries consisting of hundreds or even thousands of distinct nanoparticle formulations. We developed methods to screen these particles to identify the ones with the optimal properties for diseased-tissue targeting and avoidance of off-target tissues. Importantly, the particles we developed are composed of biocompatible and biodegradable polymers that are commonly used in other pharmaceutical products such as biodegradable microspheres and PEGylated proteins.

Zale (BIND Biosciences): BIND is now using this platform to develop targeted nanoparticles called Accurins to treat cancer and other diseases. The company has set about developing Accurins for clinical evaluation. The most advanced of these nanoparticles is BIND-014, an Accurin targeted to a cell-surface receptor expressed in all major solid tumor types. BIND-014 contains the chemotherapeutic agent docetaxel, which is a blockbuster drug in its own right, with approvals in five solid tumor indications, including breast, lung, and prostate. BIND-014 has just completed a Phase I clinical trial and is advancing into Phase II. The early results for BIND-014 are very promising. We have seen that the drug behaves very differently from conventional docetaxel, including showing signs of activity at relatively low doses and in tumors where docetaxel is not normally used.

Zhao (NTU): Our multifunctional meso-porous silica nanoparticles for cancer-targeted and controlled drug delivery have three components—the mesoporous silica nanoparticle core, the amino-β-cyclodextrin, the PEG polymers functionalized with an adamantane (Ad) unit at one end and a folate (FA) unit at the other end (Ad-PEG-FA) (18). The surface of mesoporous silica nanoparticles is firstly functionalized with amino-β-cyclodextrin rings bridged by cleavable disulfide bonds, blocking drugs inside the mesopores of the nanoparticles. The Ad-PEG-FA polymers are immobilized onto the nanoparticle surface through strong β-cyclodextrin/adamantane complexation. The multifunctional nanoparticles can be efficiently trapped by folate-receptor-rich cancer cells through receptor-mediated endocytosis, where they then rapidly release the loaded anticancer drug inside the cell when triggered by the acidic pH and intracellular glutathione.

BIND-014 has just completed a Phase I clinical trial and is advancing into Phase II. —Zale

Several functions are built onto the multifunctional nanoparticles to deliver drugs in an optimal fashion. These functions include:

- PEGylated coating on the nanoparticle surface to enhance long-term stability of the nanoparticles under physiological conditions
- Active cancer targeting by the folate ligands attached onto the nanoparticle surface
- pH-triggered drug release to allow drug released within acidic intracellular compartments such as endosome and lysosome (pH 5.0–5.5)
- Positively charged nanoparticle surface under acidic conditions to facilitate the transfer of the nanoparticles from endosome to cytoplasm
- Glutathione-induced cleavage of the disulfide bonds to further enhance the drug release in the cytoplasm of cancer cells.

The engineering of these functions onto the single nanoparticle entities significantly enhances the efficacy of anticancer drug delivery to cancer cells, while reducing the cytotoxic effects on healthy cells. *In vivo* experiments demonstrate that doxorubicin-loaded multifunctional mesoporous silica nanoparticles could effectively release doxorubicin to tumor sites resulting in significant inhibition of the tumor growth.

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Nitrogen dioxide (NO_2) gas can provide manufacturers of parenteral drug products with a truly room-temperature means of sterilizing the external surfaces of single-dose drug containers that are intended for use in a sterile field. Other sterilization options, such as ethylene oxide (EO), hydrogen peroxide (H_2O_2), and radiation, may expose the drug products to elevated temperatures over extended times or penetrate the container and closure systems. Both of these scenarios can adversely affect drug products or biologics, especially those that have limited stability at elevated temperatures. NO_2 is compatible with many of the materials that are common to parenteral drug containers and closure systems including glass, cyclic olefin copolymers (COC), polypropylene, silicone rubber, thermoplastic elastomers, and pharmaceutical rubbers. As a surface sterilant, NO_2 does not penetrate containers or closure systems during the sterilization process, leaving the drug product unaffected.

NO_2 possesses some specific chemical and physical properties that make it well positioned for use as a sterilant for pressure- and temperature-sensitive parenteral drug products. Because it boils at 21°C, the NO_2 sterilant can be introduced into the chamber with minimal to no vacuum. Sterilization is typically carried out using NO_2 concentrations that are in the range of 1–2% of the saturated vapor pressure. Because of this, condensation of the sterilant is not likely to occur, even in complicated geometries. Heating of the NO_2 sterilization chamber is not required to maintain the sterilant gas phase, which allows sterilization and aeration to be carried out at room temperature. Both EO and H_2O_2 sterilization, however, generally require some degree of heating, which can result in destabilization of sensitive products.

Heating of the nitrogen-dioxide sterilization chamber is not required.

NO_2 sterilization provides rapid and effective inactivation of both vegetative and spore forms of bacteria. This rapid lethality allows a sterility assurance level of 10^{-6} to be achieved in a cycle with a typical door-to-door time of 60–120 minutes, thereby minimizing the time that the drug product is exposed to room temperature. There is no preconditioning phase, and aeration of residual sterilant from the product is included in the overall cycle time.

NO_2 is compatible with many of the sterile barrier packaging options on the market, such as Tyvek pouches and plastic trays with Tyvek lids. As NO_2 is a surface sterilant, the gas requires access to the product, which is afforded by the breathable Tyvek. Sterilization with NO_2 would typically be carried out in the primary packaging, and any instructions for use would be included in the secondary package.

NO_2 sterilant, while a toxic gas, is non-carcinogenic and non-flammable, which makes it attractive as an option to bring sterilization onto the manufacturing floor for higher volume manufacturers. In-house sterilization offers potential savings in terms of both transportation and inventory carrying costs associated with contract sterilization. Sterilization can be placed in-line between primary and final packaging operations. For manufacturers whose volumes are not large enough to warrant on-site sterilization, yet who require room-temperature sterilization, contract NO_2 sterilization is an option. **PT**

Sterilized packages may be handled immediately after the cycle (Noxilizer, RTS 360 Industrial Nitrogen Dioxide Sterilizer).


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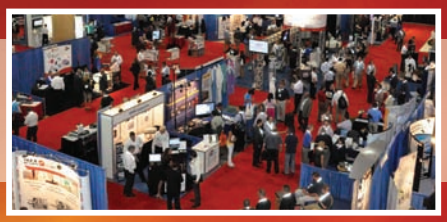

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Navigating the Global Manufacturing Supply Chain

Patricia Van Arnum

As the strategic value of emerging markets increases, pharmaceutical companies increase their R&D and manufacturing investments.

Emerging markets are an important part of the pharmaceutical majors' growth strategy. As these markets become of increasing strategic value, pharmaceutical companies are ramping up investment in R&D and manufacturing (API and finished drug product) in these areas.

Evaluating the market

Emerging markets are playing an increasingly important role in overall pharmaceutical industry growth. The global market for medicines is expected to rebound from a recent low of 3–4% growth in 2012 to 5–7% growth in 2016, according to a July 2012 analysis by the IMS Institute for Healthcare Informatics. Growth will primarily be from emerging markets as growth in established markets in the United States, Western Europe, and Japan remains weak comparative to historical levels. Overall, annual global spending on medicines will rise from $956 billion in 2011 to $1 trillion by 2013, and to nearly $1.2 trillion in 2016, representing a compound annual growth rate (CAGR) of 3% to 6%. For purposes of the IMS analysis, spending is reported as ex-manufacturer prices and does not reflect off-invoice discounts and rebates and is converted from local currencies to US dollars. Absolute growth in global pharmaceutical spending between 2012–2016 will be between $220 billion and $250 billion, compared with $298 billion in the prior five years.

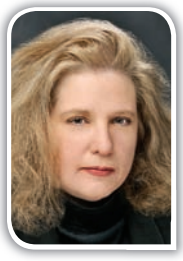
Growth in annual global spending is forecast to more than double in 2016 to as much as $70 billion, up from a $30-billion pace in 2012, driven by volume increases in what IMS terms the "pharmerging" markets and some uptick in spending in developed nations. The "pharmerging" markets are defined by IMS as countries with greater than $1 billion in absolute spending growth between 2012–2016 and that have gross domestic product per capita of less than $25,000 at purchasing power parity. Using that criteria, China is classified as a Tier-1 country, and Brazil, Russia, and India as Tier-2 countries. Tier 3-countries are Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan, and Vietnam.

IMS projects that healthcare systems in pharmerging markets will nearly double their medicine spending over the next several years. Annual spending on medicines in the pharmerging markets will increase from $194 billion in 2011 to between $345 billion and $375 billion by 2016, or $91 in drug spending per capita, according to IMS. The increase will be driven by rising incomes, continued low cost for drugs, and government-sponsored programs designed to increase access to treatments. Generic drugs and other products, including over-the-counter medicines and diagnostics will account for approximately 83% of the increase.

A BRIC focus

Among the emerging markets, the BRIC (Brazil, Russia, India, and China) countries represent the largest areas of pharmaceutical industry growth. China's pharmaceutical market was valued at $66.7 billion in 2011 and is expected to reach between $155 billion and $165 billion by 2016, representing a CAGR of 15% to 18% between 2012–2016, according to IMS. Brazil's pharmaceutical market was valued at $29.9 billion in 2011 and is expected to reach between $42 billion and $52 billion by 2016, representing a CAGR of 12% to 15% from 2012–2016. Russia's pharmaceutical market was valued at $15.7 billion in 2011 and is forecast to be between $23 billion and $33 billion by 2016, representing a CAGR of 10% to 13% from 2012–2016. And India's pharmaceutical market was valued at $14.3 billion in 2011 and is expected to reach between $24 billion and $34 billion by 2016, representing a CAGR of 14% to 17%, according to IMS.

Based on these projections, China will move into second place in the global pharmaceutical market by 2016, surpassed only by the United States, which will continue to hold the number one



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position on a global basis, according to IMS. Brazil will move into fourth place, India into eighth place, and Russia into ninth. Among developed markets, Japan will drop from the second largest global market to the third by 2016. Germany and France will each drop a notch, from fourth and fifth, respectively, in the global rankings in 2011, to fifth and sixth in 2016 as projected by IMS. Italy will stay in seventh spot in 2016, the same position it occupied in 2011. The developed markets of Spain, Canada, and the United Kingdom, respectively ranked as eighth, ninth, and tenth in 2011, will be eclipsed by Russia and India in the global rankings by 2016, according to IMS projections.

Company activity

China. The pharmaceutical majors are pursuing direct investment in R&D and manufacturing as well as partnership strategies in emerging markets (1–2). Some recent investment in China by the pharmaceutical majors includes Hisun–Pfizer Pharmaceuticals, a joint venture formed between Pfizer and the Chinese pharmaceutical company Zhejiang Hisun Pharmaceuticals with the aim to develop, manufacture, and commercialize off-patent pharmaceutical products in China and other markets. In May 2012, Sanofi inaugurated a new assembling and packaging line for producing its prefilled insulin injection pen Lantus SoloStar at its facility in Beijing. The company announced a second phase $90-million project to install a cartridge aseptic product line at the facility.

Novartis has been actively building its position in China. In 2007, Novartis opened a start-up facility for a new R&D center in Shanghai, China, and broke ground in 2008 on Phase I of a new facility that was originally to be home to approximately 400 R&D scientists and approximately 400 other pharmaceuticals division personnel. In 2009, it expanded the scope of the site with plans to invest $1 billion during the next five years to increase the size of its operations in Shanghai. Based on a re-evaluation of the site conducted in 2010, the current Phase 1 has been extended by two buildings. The cross-divisional Shanghai campus will house 800 offices and 400 laboratory workplaces

In 2012, Eli Lilly opened a new diabetes R&D center in Shanghai. The center employs 150 scientists and staff hired primarily from China. Eli Lilly also is constructing a new insulin production, packaging, and warehouse facility in Suzhou, China, which was schedule to open in late 2012. In June 2012, Eli Lilly announced an expansion of its manufacturing capabilities in China through an expanded collaboration with Novast Laboratories, a generic-drug and specialty pharmaceutical company based in Nantong, China. The collaboration will enhance Lilly's efforts to build a portfolio of Lilly branded generic medicines in China, and eventually may be used to provide regional manufacturing support for Lilly's pipeline of products in development.

For Roche, a key project included transforming its manufacturing facility for solid dosage forms in Shanghai from a local to a global supply operation. In early 2011, the facility received FDA and EMA approvals to produce Xeloda (capecitabine) for the US and EU markets.

Russia. Unlike other BRIC countries, such as India and China, which have a domestic manufacturing base, Russia is largely dependent on pharmaceutical imports. Its domestic biomedical industry accounts for only 0.2% of the global market, but the country is committed to change that level through an ambitious program, Pharma 2020. Pharma 2020, a state-initiated plan, seeks to boost output of local medicines from 25% of gross sales in 2010 to 50% by 2020, upgrade domestic pharmaceutical manufacturing operations to GMP standards, and increase the level of innovator pharmaceuticals in the Russian market (3). Several pharmaceutical majors are increasing their presence in Russia with manufacturing and R&D investment (1–2).

In September 2012, Takeda Pharmaceutical completed construction of a

Inside view: Drug, Chemical and Associated Technologies (DCAT)– DCAT Week 2013

DCAT Week, organized by the Drug, Chemical and Associated Technologies Association (DCAT), is a much anticipated event for fine-chemical producers, contract manufacturers, and pharmaceutical/biopharmaceutical companies. In 2013, DCAT Week is being held Mar. 11–14 in New York. In addition to the annual dinner, which is being held on Thursday Mar. 14, a key part of DCAT Week is the educational programing, which is designed to provide useful and practical information to pharmaceutical/biopharmaceutical companies and their suppliers.

The educational programming kicks off on Monday Mar. 11, with a *PharmaChem Outlook*, presented by IMS, which will provide an overview, critical insights, and data on the impact of the sustained recession in mature markets and the extent to which expansion in emerging markets can potentially compensate for the low growth being experienced in North America, Europe, and Japan. Forecasts on a global and regional level, segmented between innovator brands and generics drugs, will provide insight into the growth patterns for pharmaceutical companies and their suppliers. On Tuesday, Mar. 12, a session on the implications of the Generic Drug User Fee Act (GDUFA) will be held. GDUFA was designed to speed access to safe and effective generic drugs by requiring the industry to pay user fees to supplement the costs of application review, facility inspection, and backlog reduction. Part of the requirements of GFUDA involves fees on API manufacturing sites and Type II drug master files. Industry regulators and manufacturers involved in the creation of GDUFA will provide further insight into the implementation of the law, related procdures, and requirements. Other sessions on Tuesday Mar. 12 will discuss the following: excipient innovation for bioavailability enhancement; collaborative approaches in supply-chain security; continuous-flow processing for API manufacturing; and regulatory and technical developments in track-and-trace methods. On Wednesday, Mar. 13, sessions will focus on outsourcing of sterile manufacturing , large-molecule drug delivery, and developments in single-use technologies.

Additional information on the educational programming during DCAT Week 2013 may be found at www.dcat.org.

EUR 75 million ($99 million), 24,000-m^2 pharmaceutical manufacturing facility in Yaroslavl, Russia. The plant, which is approximately 280 kilometers from Moscow, is one of the first by a major multinational company in Yaroslavl's pharmaceutical cluster. The facility is expected to be fully operational by 2014.

The Yaroslavl facility will enable Takeda to meet demand in Russia initially for several products: Cardiomagnyl (acetylsalicylic acid and magnesium hydroxide), Actovegin (derived from calf blood), and calcium tablets. The plant will have the initial capacity to manufacture 90 million sterile ampuls and more than two billion tablets per year. Liquid-sterile production includes solution preparation, washing of ampuls, sterilization, filling, inspection, and packaging. Solid production will encompass all stages, from weighing, mixing, and granulation through compression, coating, and packaging. Takeda estimates that it is the seventh largest pharmaceutical company in Russia and expects company annual growth rate of 15% in Russia through 2016.

In April 2012, Novo Nordisk broke ground on a new $100-million plant in Russia that will formulate and fill insulin into Novo Nordisk's Penfill cartridges and pack the FlexPen prefilled insulin delivery device for the Russian market. Located in Grabtsevo Technopark in the Kaluga region, the plant is expected to start manufacturing in 2014. The company's intention to establish insulin production in Russia was first announced in 2010. At that time, an agreement of cooperation between the government of the Kaluga Region and Novo Nordisk was signed. Sanofi also recently increased insulin capacity at its facility in Orel, Russia. Sanofi obtained the facility following its acquisition of a controlling stake in the pharmaceutical company Bioton Vostok in 2010.

Novartis is proceeding with a new $140-million manufacturing plant for pharmaceuticals and generic drugs in St. Petersburg, Russia. The plant is expected to produce approximately 1.5 billion units per year (oral solid dosage forms). The greenfield facility is in the Novoorlovskaya Special Economic Zone located to the north of the St. Petersburg city center. Novartis began construction of the facility in 2011. The facility is expected to be completed and approved for commercial production in 2014.

The facility is part of a five-year, $500-million investment into Russian healthcare infrastructure announced by Novartis in December 2010. This plan addresses three core areas: local manufacturing, R&D collaborations, and public health development in Russia. These activities include collaborations with academia and emerging Russian private businesses in different areas of medical science. The scope of these collaborations may include efforts, such as out-licensing of Novartis compounds to Russian companies with proven scientific capabilities, in-licensing and scouting for promising drug candidates from Russian scientists and universities, and modeling and simulation activities for clinical trials. Novartis is working in all of these areas to identify high potential projects to be jointly developed. Additionally, Novartis also has made a commitment to double its investments in drug development in clinical trials in Russia and expects to enroll approximately 4000 individuals by 2013, said the company in announcing its plans in December 2010.

Russia's Pharma 2020 project is designed to increase domestic pharmaceutical production.

In 2011, AstraZeneca announced plans to establish a Predictive Science Center in St. Petersburg, the company's first such center in Russia. The center will focus on developing bioinformatices, data-analysis methods, software, and systems to evaluate safety and efficacy of new drugs. Approximately 30 people will be employed at the center through local collaborations and organizations. Also in 2011, AstraZeneca began construction of a new $150-million manufacturing facility in the Kaluga region in Russia to supply locally produced medicines. The company also has partnerships with several R&D institutes in Russia, including the Skolkovo Innovation Center and Russia Venture Company, for research and clinical trials.

In July 2012, Pfizer granted exclusive development and marketing rights to the Russian firm SatRx for its dipeptidyl peptidase-4 (DPP-4) inhibitor PF-00734200 for Type 2 diabetes. SatRx, which is part of the ChemRar Hi-Tech Center, received worldwide rights (excluding China) to the drug as a monotherapy or in combination with other diabetes drugs. Pfizer will receive royalties and milestone payments based on commercialization activities. The agreement was developed as partial fulfillment of a memorandum of understanding reached in March 2011, under which Pfizer and ChemRar agreed to explore collaborations focused on research, development, and commercialization of compounds and vaccines to treat cardiometabolic, infectious and oncologic diseases in Russia and other countries.

In 2010, GlaxoSmithKline formed an alliance with JSC Binnopharm for the local secondary manufacture of several GSK vaccines. Under this alliance, which was announced in November 2010, GSK is supplying bulk vaccine and providing technology and expertise to enable Binnopharm to undertake the secondary manufacture, including filling and packaging of GSK vaccines. Binnopharm will be responsible for gaining approval of their facilities to allow supply of GSK cervical cancer, rotavirus, and pneumococcal vaccines under Binnopharm's trademark for the Russian public market.

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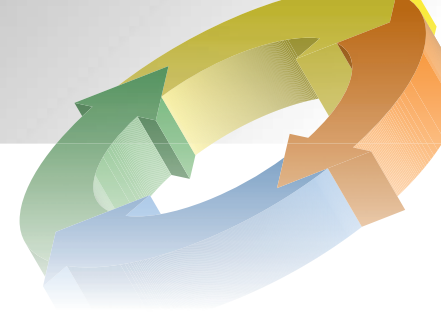

Isolation of Pharmaceutical Impurities and Degradants Using Supercritical Fluid Chromatography

Jeffrey P. Kiplinger, Paul M. Lefebvre, Michael J. Rego, and John H. Tipping

Isolation of trace impurities and degradants from mixtures containing primarily an API, or an API plus excipients, is often necessary for structure elucidation purposes. Using chromatographic methods for this purpose can be a slow and painstaking work. The authors demonstrate that using supercritical fluid chromatography (SFC) offers distinct advantages in speed and in clean isolation of the desired peaks. These advantages are derived from the rapidity of method development, the efficiency of the preparative fractionation, and the ease with which commonly used reversed-phase high-performance liquid chromatography data may be correlated with SFC. Case studies are used to illustrate these efficiencies.

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Chromatographic isolation of degradants and impurities, whether from stressed lots of pharmaceutical compounds or directly from the API, is often required when their structures are unknown and/or reference standards cannot be prepared by synthesis (1). Isolation of these (often trace) components can be a painstaking process for analytical laboratories that involve, even in the simplest scenarios, many repeated injections of material on a chromatographic column to accumulate the trace component chromatographic peak. Often the peak of interest is profiled using a stability-indicating method designed for optimum resolution of all possible impurities and degradants (2, 3). Adapting this method to preparative scale consumes huge quantities of solvent, has a long cycle time that slows accumulation of the trace component, and requires that large amounts of accumulated solvent be removed to recover a few milligrams of the peak in quantity sufficient for structural analyses using nuclear magnetic resonance (NMR) and multiple and sequential mass spectrometry (MS^n).

Using supercritical fluid chromatography (SFC) (4) in place of traditional reversed-phase and normal-phase high-performance liquid chromatography can greatly reduce the timelines for this process. Both the rapid method development cycle in SFC and the high efficiency of preparative SFC separations contribute to the reduced timelines (5). Solvent consumption is also reduced because SFC uses a mixed phase of solvent and recycled carbon dioxide (CO_2). The accumulated fractions from SFC chromatography are highly concentrated compared with those collected with conventional liquid chromatography. In addition, the lability of compounds collected during the isolation process may be minimized in common SFC solvent systems and by the mild and fast evaporation conditions used for such highly concentrated fractions.

SFC methods, however, are not commonly developed as stability-indicating methods. SFC is a normal-phase chromatography, and most stability-indicating methods use reversed-phase high-performance liquid chromatography

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Figure 1: Reversed-phase high-performance liquid chromatography (UV 260 nm, Method A) of the API showing known and unknown impurities. The unknown impurity (0.5% by relative absorbance) is observed at 9.7 min.

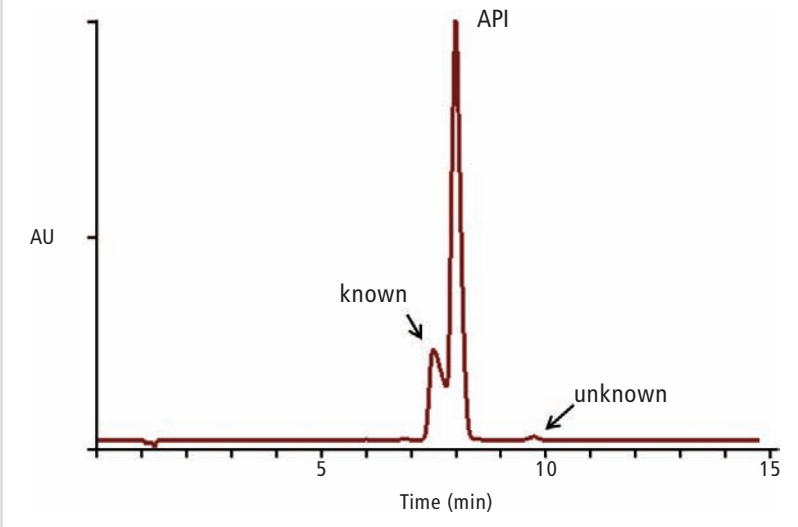
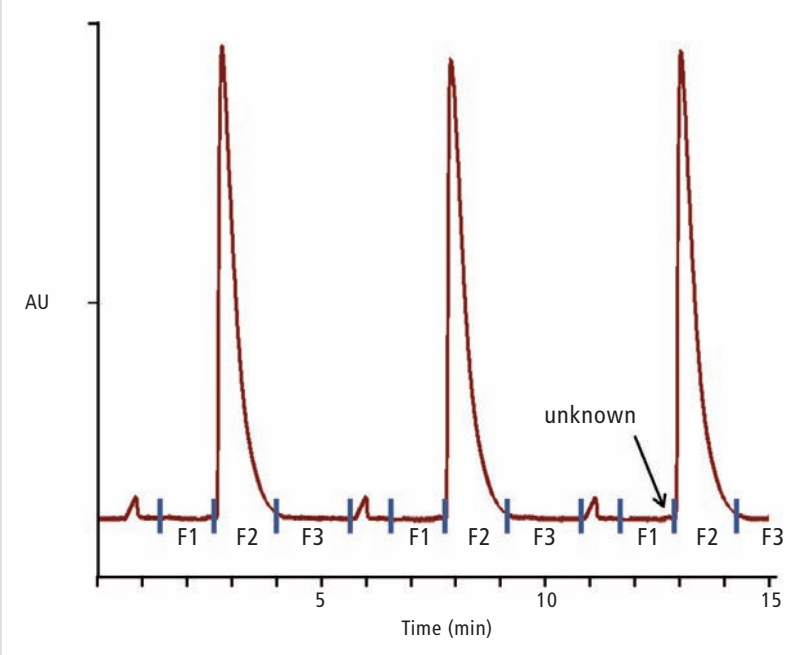


Figure 2: Preparative supercritical fluid chromatography (UV 260, Method B) chromatogram, showing the fractions collected to enrich the target impurity. The target elutes in fraction F1.



(RP-HPLC). SFC methods must be developed *a priori* for isolation work. Using SFC as an isolation technique requires some investment in equipment, often in columns; however, the benefits to the pharmaceutical development process can be significant for a laboratory accustomed to RP-HPLC approaches.

Methods and materials

All instrumentation used in this work was acquired from Waters Corp. The systems included Thar AMDS analytical SFC systems, Thar Prep80 preparative SFC systems, Waters Alliance 2795 HPLC systems, Waters 996 photodiode array detector, and Waters ZQ single quadrupole mass spectrometry (MS) detector. All solvents were HPLC grade. Buffers and solvent additives were supplied by Sigma-Aldrich. Column sources are indicated with the specific methods as further described.

Enrichment. Method A. The RP-HPLC method to identify and assign purity to the target impurity isolate used a Halo C18 4.6 x 150 mm 2.7-µ column (Mac-Mod Analytical). Solvent A was water (0.1% trifluoroacetic acid [TFA]). Solvent B was acetonitrile (0.1% TFA). The solvent gradient was 17% B over 12 min, 17–100% B over 3 min, 1-min hold, and 3-min recycle. The impurity at 9.0 min has an enhanced absorbance relative to the main peak when detected at 260 nm.

Method B. The intermediate SFC method to collect an enriched fraction used an (*S,S*) Whelk-O1, 30 x 250 mm, 5-µ column (Regis Technologies). The preparative method was isocratic, 10% methanol in CO_2 at 80 g/min and 120 bar pressure; 300 mg of feed were injected every 2.1 min for a productivity rate of 8.5 g/h.

Method C. For final purification of the target from the enriched sample, a new SFC method was developed using a RegisPack 4.6 x 100 mm 5-µ column (Regis Technologies). The isocratic method used 13% methanol:isopropanol (50:50) in CO_2; 240 mg of enriched fraction were processed in eight injections over 30 min.

Direct Isolation. Method D. The client's HPLC method was used to assess the stress degradation mixture, using a Waters XBridge Phenyl 4.6 x 150 mm 5-µ column. Solvent A was 10 mM ammonium formate in water adjusted to pH 4.0. Solvent B was 10 mM ammonium formate in methanol:water (90:10) adjusted to pH 4.0. The gradient elution at 1 mL/min used a solvent gradient 10–40% B over 30 min, 40–100% B over 5 min, and 4-min hold.

Isolation strategies

Two isolation strategies are commonly used in the authors' laboratory—enrichment and direct isolation. In the enrich-

ment strategy, an SFC method is developed that appears to resolve the main peak (usually the active ingredient) from neighboring peaks, and the main peak is captured and removed to produce an enriched fraction containing all other compounds, including the desired degradants. This approach takes advantage of the speed with which SFC can process a feedstock solution of the sample and can be used even when the trace target peak(s) is/are not visible under preparative chromatography conditions due to limited detection range at high loads. Using the direct-isolation strategy, a specific SFC method is developed that resolves the desired trace peak, and that peak is collected as a purified isolate. This approach requires that the desired peak be visible with a specific detection signature (e.g., a specific UV absorbance wavelength or a mass not shared by other compounds in the mixture). Enrichment and direct isolation are frequently used together, and complex projects involving multiple isolates may require their sequential application. For example, once an enriched fraction containing the desired peak is obtained, the desired peak is often an abundant component in a fraction that becomes a small feedstock fraction for direct isolation.

In the authors' laboratories, a process termed "targeted isolation" is used to rapidly develop methods for purification of single peaks from complex mixtures. Targeted isolation involves linking specific information, such as the UV absorbance spectrum or mass spectral data acquired in RP-HPLC analysis, to normal phase SFC chromatograms. This approach is used to cross-correlate peaks as analysts rapidly develop SFC methods—initially, gradient elution and finally, isocratic methods, to be scaled to preparative chromatography. While this article does not discuss all the aspects of targeted isolation, the parts of the process used to "close in" rapidly on the peak of interest are discussed. Case studies that illustrate these strategies and discuss the merits and advantages of SFC technology in their application are presented.

Case study 1: enrichment

A client API contained two process impurities—one identified and one unknown. Both were visible by UV detection at 260 nm, a wavelength at which the API absorbs light less strongly. Thus, the relative absorbance chromatogram observed in the straightforward gradient RP-HPLC method (Method A, see **Figure 1**) was known to overrepresent the true abundance of both impurities. The unknown impurity had a relative absorbance of 0.5% and a true abundance estimated at less than 0.2%. Preparative isolation by scaling up Method A was rejected due to time, solvent consumption,

Figure 3: a (left): Reversed-phase high-performance liquid chromatography (Method A) chromatogram of enriched fraction. b (right): Analytical supercritical fluid chromatography (Method C) chromatogram of the enriched target, showing remaining active and other impurities. The mass spectrum for target at m/z 385 is identical for the indicated peaks in each chromatogram.

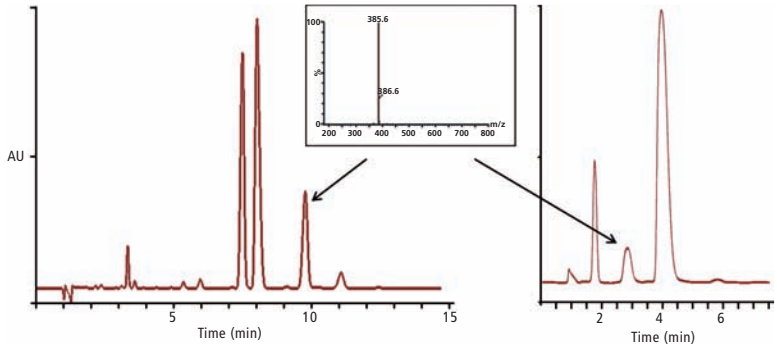
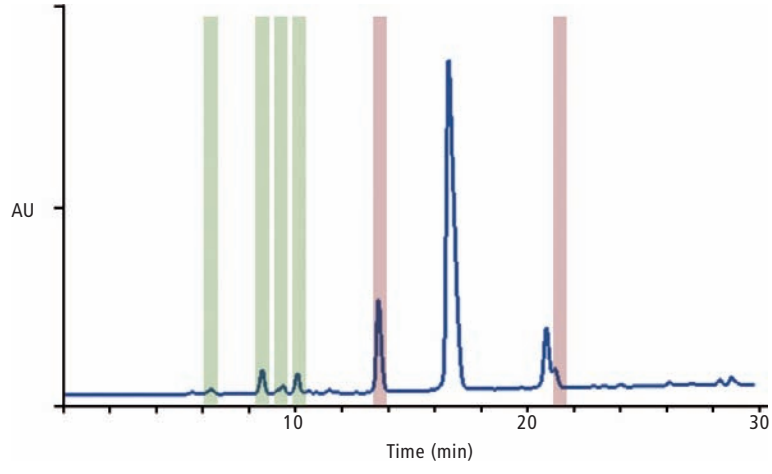


Figure 4: Reversed-phase high-performance liquid chromatography (UV detection 295 nm, Method D) of degradant-enriched sample, showing primary (light red) and secondary (light green) purification target peaks.



and the excessive fraction volumes that would be accumulated in the isolation of this low-abundance peak. It was hoped that, by using SFC methods, the target impurity could be recovered more expediently in the milligram quantities desired for a complete or partial structure elucidation by 2D NMR and MS^n methods.

Under preparative SFC conditions with detection at 260 nm, the impurity peak signal was difficult to identify unambiguously. A preparative SFC method (Method B) was developed quickly and used to process several grams of API, with fractions collected before, during, and after the main peak eluted. These fractions were concentrated by rotary evaporation and analyzed using the RP-HPLC method for the presence of the desired peak. The desired peak was captured and enriched in a fraction collected immediately before the main peak, indicating that the chosen SFC method adequately resolved the peak from its neighbor. To accumulate the target peak in quantity sufficient for structural work, 50 g of the API were injected during a period of 7 h of automated stacked injection chromatography (see **Figure 2**) to produce a highly enriched fraction with a total mass of 240 mg (see **Figure 3**).

Method C, which involves direct isolation of the target peak from the enriched fraction, was developed by screening multiple SFC conditions in an automated method-development process. Typically, several hundred solvent and stationary phase pairings can be screened in an overnight series of gradient runs, and a promising separation may be converted within a few minutes to a preparative-scale isocratic process. In this case, the target peak was identified based on its relative abundance in the HPLC chromatogram in **Figure 3a**, and a method resolving the target completely from its near neighbors was chosen (see **Figure 3b**). The 240-mg enriched isolate was dissolved in the liquid cosolvent and processed in less than 1 h to isolate the desired compound. Evaporation of approximately 50 mL of collected solvent yielded 14 mg of the pure target peak.

The development of a controlled and well-characterized production process for a new drug is a complex task. The client producing this API estimated that the identification of this trace impurity, efforts to synthesize it based on various hypotheses about its source, attempts to remove it by chemical methods or through alternate synthetic approaches, and attempts to recover it through chromatography would take 12–14 months. Isolation of the compound using SFC required less than a week, and its structure was determined by NMR and MS.

Case study 2: direct isolation

A stress degradation product was partially purified by low-pressure chromatography to remove much of the remaining main drug peak. The degradant-enriched mixture had two significant peaks of interest (primary targets) and several of minor abundance (secondary targets), in addition to components not of interest to the chemistry team. The HPLC chromatogram of the mixture is shown in **Figure 4**. The goal for the isolation was to capture cleanly each of the primary targets for structure elucidation and to capture the

secondary target peaks if it were not "overly difficult." Preparative RP-HPLC was undesirable due to poor loading and excessive processing time.

The development of an SFC method specific for a targeted minor component is often complicated by the lack of availability of an SFC method identifying the peak of interest. Frequently, stability-indicating methods identifying minor API components are RP-HPLC gradient-elution methods. Thus, the initial phase of method development is aimed at identifying the peak of interest in an SFC chromatogram, followed by an optimization phase to resolve that peak from its neighbors. The final isocratic method is scaled to a preparative column so that the peak may be accumulated by injection stacking.

To facilitate the sometimes difficult process of correlating the peak in the RP-HPLC method with SFC, the authors previously developed a co-configured HPLC/MS and SFC/MS system (6) that uses the same mass spectrometer as a detector for either chromatography. Using this system, masses can be assigned to mixture components in both the RP-HPLC trace and the SFC chromatogram. This cross-correlation of orthogonal reversed-phase and normal-phase peak profiles, and the subsequent development of an appropriate preparative chromatography method to cleanly capture a target peak is part of the targeted isolation process. The standard HPLC method is still used to confirm the successful isolation of each component (see **Figure 3**).

This approach to separation is straightforward, but appears cumbersome at first glance. Due to the rapidity with which isocratic SFC methods may be developed, there is little need to spend time and effort to develop an optimal

Table I: Supercritical fluid chromatography methods used in the target peak isolation tree, numbered according to Figure 5.

Method	Column	Cosolvent	Cosolvent %	Flow Rate (g/min)	Pressure (bar)	Temperature (°C)
1	2.1 x 25 cm PVA-Sil*	Isopropanol:methanol (1:1) with 1% isopropylamine	65	45	100	25
2	2.1 x 25 cm PVA-Sil*	Isopropanol with 1% isopropylamine	50	45	100	25
3	2.1 x 25 cm (S,S) Whelk O-1**	Isopropanol:methanol (1:1) with 1% isopropylamine	45	80	100	25
4	2.1 x 25 cm Pyridyl Amide+	Isopropanol:methanol (1:1) with 1% isopropylamine	55	60	100	25
5	2.1 x 25 cm PVA-Sil*	Ethanol with 1% isopropylamine	55	45	100	25
6	2.1 x 25 cm (S,S) Whelk O-1**	Methanol with 1% isopropylamine	35	80	100	25
7	2.1 x 25 cm PVA-Sil*	Methanol with 1% isopropylamine	45	80	100	25
8	2.1 x 25 cm AD-H++	Isopropanol with 1% isopropylamine	30	80	100	25
9	25 cm x 20 mm Amino Phenyl+	Isopropanol with 1% isopropylamine	35	80	100	25

* Column from YMC Americas, Allentown PA
** Column from Regis Technologies, Morton Grove IL
+ Column from ES Industries, West Berlin NJ
++ Column from Chiral Technologies, West Chester PA

method first. A complex sample may be sectioned into several fractions (in this case four), which are then examined using the standard HPLC method for the presence of one or more of the targets. Once a fraction contains only a few components, the target peaks often can be selected based on relative abundance, mass (as measured by the MS detector), or by a specific UV signature. Highly specific methods are then developed to cleanly resolve the targets. At the end of a multicomponent isolation project, a method and fraction tree illustrates the work flow of the complete separation (see **Figure 5**). Individual isolates highlighted in the figures were assayed using **Method D**, and deemed sufficiently pure for structure elucidation.

The SFC methods needed to isolate the targets are detailed in **Table I**. The seeming complexity of the process is belied by the speed with which the work was accomplished—in this case, less than three weeks of effort during a period when concurrent project work also demanded laboratory resources. The rapidity derives from the efficiency of method development, processing, and recovery from liquid fractions when using SFC; all of these facilitate the rapid cycle time from peak to method to isolation.

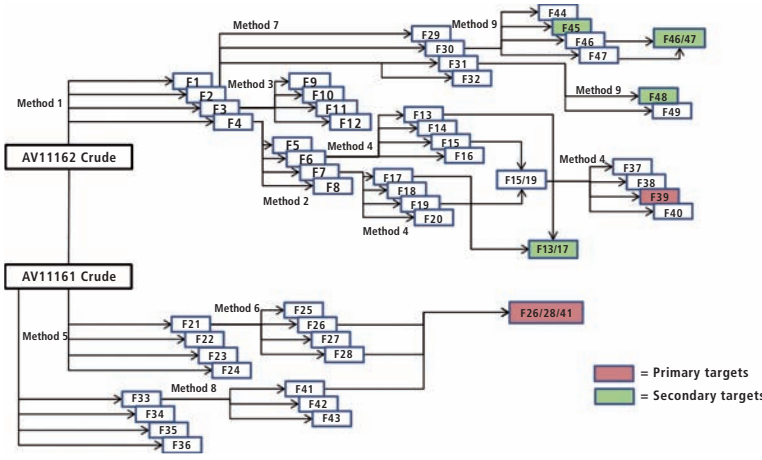
Discussion

The two strategies take advantage of different key attributes of SFC. The enrichment strategy leverages the speed of processing in SFC versus HPLC, achieved through increased loading, narrow bands, and high linear solvent velocities. SFC has often been described as 3–10 times faster than HPLC (5).

The direct isolation strategy leverages the processing speed advantage as well, but in comparison with HPLC, the speed of method development offers a significant additional process enhancement. To achieve the same resolution in HPLC, one frequently uses a longer column with a higher plate count. In SFC, the linear mobile phase velocity is 8–20 times that of an equivalent HPLC method, as short columns and high flow rates are both commonly used in method development and these methods are arithmetically scaled to larger column formats (7). Moreover, this translates into extremely fast column equilibration times, meaning that as many as 20 different SFC methods may be evaluated for every one HPLC scouting run. In addition, it was observed that the highly concentrated fraction volumes in SFC offer a significant advantage, i.e., the ability to quickly remove solvent and analyze the isolate significantly speeds the cycle through processing and method development.

Finally, it was noted that the lack of oxygen and water in the SFC solvent environment limits many common degradative pathways that would otherwise prevent the capture of certain primary degradants. Less nucleophilic alcohols, such as isopropanol and the butanols, usually offer good selectivity and have been used when methanol reactivity is a concern. SFC may offer a greater chance of success when the goal is to isolate primary degradants intact without secondary decomposition.

Figure 5: Method development and fractionation tree for the recovery of the targets identified in Figure 4.



Conclusions

SFC is, in many ways, an ideal tool for facilitating trace component capture and analysis. Scalable separations are developed rapidly, large amounts of feed may be rapidly processed, dual strategies may be used exclusively or combined, and milligram quantities of highly pure isolates can be accumulated for structural or biological assays. In addition, the solvent environment is much more benign than conventional chromatography approaches.

SFC can be superior to conventional chromatography approaches in many cases, and should be considered by laboratories. Given the complex nature and long timelines of these projects, and the scale of chromatography that must be undertaken to access trace components, it is worth the effort to identify the best approach to such challenging separations problems.

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Foam Granulation

A New Approach to Continuous Wet Granulation Using a Twin-Screw Extruder

Michael R. Thompson and Paul J. Sheskey

As a result of changing philosophies towards continuous manufacturing, new equipment is being introduced into pharmaceutical production facilities. The twin-screw extruder is an example of such equipment for use in wet granulation. The authors review developments in wet granulation using a twin-screw extruder; lay out the issues with wetting in this machine; and introduce a novel technique, foam granulation, that uses the twin-screw extruder to fully satisfy the unique needs of granulation.

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The twin-screw extruder provides highly consistent granulates due to its continuous operation and closely confined flow path, which requires that all particles experience a similar shear history. The intensive mixing of the twin- screw extruder allows lower optimal liquid concentration for granulation while producing denser granules for both placebo formulations and highly dosed drugs in comparison to a high-shear batch mixer (1, 2). As a result, drying and milling operations may be significantly reduced with use of this machinery in solid oral-dosage production.

The binding liquid in wet granulation has a profound influence on product granule properties (3–5) and affects the friction between conveyed powders and the barrel wall inside the extruder, which affects power consumption and the exiting temperature of granules (2, 6). There are crucial issues to be solved in regards to introducing liquids into this type of machinery to obtain rapid and uniform wetting of excipients so that the process exhibits stability in operation, boundaries become immediately lubricated to reduce equipment wear and granule heating, and high quality granulates are obtained.

Twin-screw extruder function

A common variant of extruder used for granulation is the fully intermeshing, co-rotating twin-screw extruder (7). Differences between vendors are largely based on the available internal volume of the machine (often described by the ratio of the outer diameter to inner diameter of screw elements) as well as the screw diameter, both of which can significantly affect granulate properties in both granule size and intragranular porosity (8). The machine is highly modular, making it a flexible platform for continuous manufacturing of different products during its lifetime of service to a company. The intermeshing region between the two screws creates a self-wiping action that minimizes material accumulation within the machine but also provides a complex flow path for powders to mix and consolidate. For wet granulation, the die end of the extruder is generally open to collect granules without excessive consolidation.

Wet granulation inside the co-rotating twin-screw extruder is a starve-fed process, meaning that the available internal volume of the machine is never completely filled with material during operation. This *modus operandi* is important to extrusion because it minimizes dissipative heat build-up in conveyed drug formulations as it limits compression against the barrel wall, it decouples the parameters of output rate

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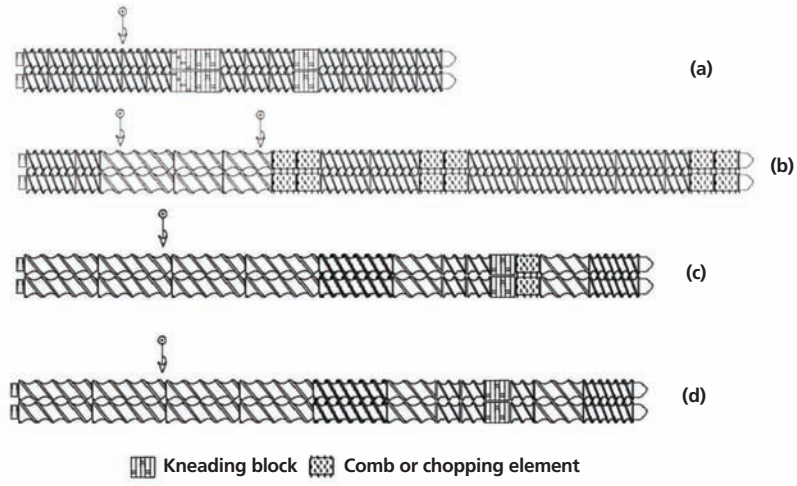
and screw speed to give formulators more control over their process, and it more readily allows the downstream addition of materials (solids, liquids, or gases) because the system is not pressurized except for small mixing regions. The zones of the screws that are starved experience dominant drag flow, in which powders are pushed downstream by the rotating flights of conveying-type elements. These screw elements have been found to contribute little to granule growth (5, 9). In fact, screw designs using only conveying elements show very poor distribution of the binding liquid within exiting solids (10). It is rare, however, that a screw design is completely comprised of conveying elements or that the entire length of the machine is ever fully starved. Significant granule growth requires the inclusion of pressure-driven mixing zones, which are necessarily fully filled as powders are squeezed through these sections. Kneading blocks and comb (i.e., chopping) elements are examples of mixers commonly used in sparing numbers along the screw length to produce granule growth along with minor attrition (5, 9, 11–13). **Figure 1** shows some typical designs for granulation. Keeping these mixing elements closer to the end of the extruder reduces attrition (4).

Figure 1: Characteristic screw designs used in twin-screw extruders for wet granulation. Screws displayed correspond to literature referenced in this article: (a) ref. 11, (b) ref. 4, (c) ref. 6, and (d) ref 6. Powders enter at the extreme left-hand side and arrows indicate points of liquid addition.



ALL FIGURES ARE COURTESY OF THE AUTHORS.

Figure 2: Typical equipment layout for foam granulation showing: (1) twin-screw extruder, (2) powder feed-port, (3) gravimetric feeder for powder excipients, (4) side stuffer, (5) mechanical foam-generator, and (6) foam feed-tube.

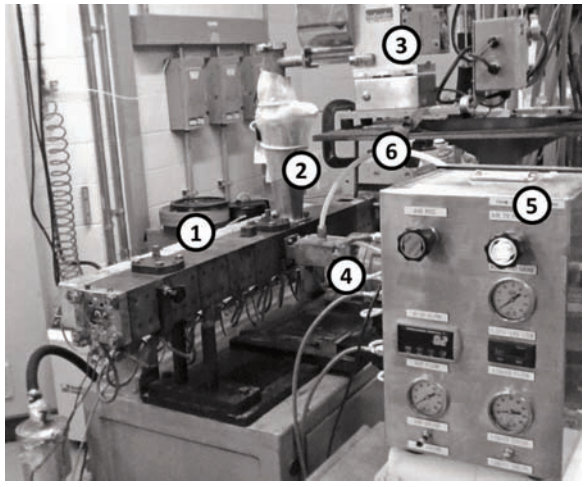
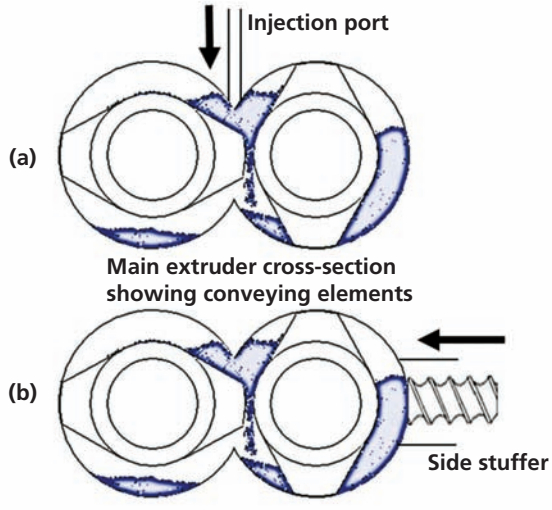


Figure 3: A cross-sectional view of the twin-screw extruder partially filled with powder excipients (in blue) shows the differences in configuration used for (a) directly injecting liquids versus (b) introducing foamed binder into the granulation process.



Powder flow rate is one of the most significant parameters influencing the extent of granule growth, with higher outputs producing larger granules. The effect is caused by the higher volumes of powder that build up in front of pressure-driven mixing zones as flow rate increases, producing larger axial compressive forces on the particles present. In fact, it has been shown that the dispersion of binder within poorly wetted mass can be improved for granulation if the screw design and flow rate are adjusted to provide appropriate compressive forces (6). The influence of flow rate on granule growth, however, is not often seen in smaller extruders or highly starved processes (4). Increasing screw speed has less influence on granule size but generally increases the number of chopping events provided by mixing zones to reduce the occurrence of oversized particles (4, 6, 9). For a fixed flow rate, increasing the screw speed will reduce the volume of powder that fills the conveying screw elements, resulting in lower power consumption by the process.

Among the published studies for wet granulation, a crucial point that is rarely mentioned, yet widely known to the pharmaceutical industry, is the difficulty of uniformly wetting a formulation in an extruder. The problem arises due to the earlier mentioned closely confined space inside the extruder, which results in the liquid injection port being in immediate proximity to the powder flow. This confinement prevents atomization of the binder solution into micro-sized droplets prior to contacting the powder solids, as is done in high-shear batch mixers. As a result, regions of the powder become oversaturated while others remain virtually dry. This issue was highlighted in the industrial-oriented article by Shah, who reported process surging, though motor overload events are also common (11). Shah demonstrated several strategies related to screw design and the sequential addition of smaller liquid quantities into the process as means to minimize surging occurrences. Such changes greatly increase the complexity of operating the extruder and do not eliminate the root cause of the problem. Alternatively, a new solution called foam granulation uses the unique behavior of aqueous foam to cause rapid spreading of the binding liquid over a large area of the powder during wetting.

Foam granulation

The aqueous foamed binder used in foam granulation is comprised of a high volume of gas dispersed within a liquid containing foamable excipients, thus forming an unstable, semi-rigid structure. Effective excipients for pharmaceutical granulation are cellulose-ether species that promote high foaming activity and act as binders in the process. Many approved nonionic, polymeric excipients are also suitable foaming agents. The foam liquid may include additives (e.g., polymeric species for binding or coating and particles, such as APIs, glidants, and disintegrant aids) as long as they do not interfere with its preparation. Semirigid foams characteristically exhibit closely packed bubbles or a polyhedral morphology depending on the gas-volume fraction although a minimum of 64% (v/v) gas is required for the foam to display some degree of rigidity. The volume fraction of gas present in foam is often referred to as its foam quality (FQ). For granulation, FQ is generally kept in a range of 75–95%. Foams that are too wet (< 75% FQ) lack adequate stability to spread well and often simply collapse on the surfaces of processing equipment. Very dry foams (> 95% FQ) occupy very large volumes of space (which complicates their addition into the confined process); exhibit very high inherent viscosities (as much as 10^5 times that of its contained liquid); and more readily collapse in the presence of shear than wetter foams (14).

Foam granulation was first introduced by Keary and Sheskey for high-shear batch mixing of pharmaceutical ingredients (15). This study demonstrated that less binding liquid was required and that the rate of foam addition could be much higher in comparison to spray wetting. The lower requirements of binding liquid were explained in the static-bed penetration studies of Tan *et al.*, which looked at saturation characteristics of foam versus dropwise wetting with lactose and glass ballotini powders (16). These studies observed that more binder mass was absorbed by these powders by foam as opposed to dropwise addition at any given time, and as a result, granule nuclei were 40% larger. Foams of higher FQ were more slowly absorbed due to slower foam coarsening and slower drainage of its contained liquid into contacting powder (14, 17). Several studies of foam granulation for high-shear batch mixers have been reported (17–21).

Continuous foam granulation with a twin-screw extruder was introduced in a case study comparing the technique to the conventional liquid addition method (6). A successful methodology to metering such foam into the machine required recognizing its solid-like behavior and using approaches commonly employed for feeding bulk solids rather than liquids. An auxiliary unit, known as a side stuffer to the extrusion industry, was found suitable for feeding foam. The side stuffer is readily available commercially, and the physical setup and control software of most extruders can be configured to accommodate it. A typical extrusion setup with the side stuffer and foam generator is shown in **Figure 2**. The side stuffer is a miniature, twin-screw auger that mounts to the side of the main extruder and conveys materials into a specified zone of the process. Due to the drag-flow action of the rotating screws in the side feeder, foam is forced into the passing formulation within the main extruder and partially collapses upon contact, while the remaining foam forms a layer between the powder and extruder barrel. **Figure 3** highlights the conceptual differences between liquid injection and foam addition from a cross-cut view of the extruder. The mechanism of foam wetting inside the extruder is still under study. A two-stage model proposed in a recent publication was based on how foams prepared from liquids of different viscosities and having different FQ collapsed and drained under different shear conditions as well as how they affected granule properties from the extruder (14). A pressure-driven wetting stage is thought to occur at the point of entry where the foam enters the process, with stiffer foams showing greater resistance to immediately collapsing upon contacting the non-wetted formulation. The remaining, uncollapsed foam pushes the powder aside to form a layer above. The subsequent shear-driven wetting stage appears governed by the response of foam to shear; layers of stiffer foam collapse more readily under mechanical shear to wet the

Table I: Differences between foamed and liquid binder addition on granulation.

Foamed binder addition	Liquid binder addition
Acceptable granulation at 6% and 11% binder concentrations	Acceptable granulation only at 11% binder concentration
Low axial compression preferred, otherwise excessive aggregation observed	High axial compression required, otherwise lactose exited as a few large, wet lumps within a matrix of dry powder
Exiting granule temperature largely insensitive to process (less than 40 °C in all cases)	Very high granule temperatures occurred (reaching as high as 90 °C at high axial compression conditions)

powder beneath while wetter foams show greater resistant collapse under mechanical shear by establishing more stable morphologies comprised of smaller bubbles.

From a practical, operational standpoint, the method of foam granulation:

- Avoids process surging in a twin-screw extruder due to the high coverage area of foam over the powder during wetting
- Simplifies process start-up because full operation rates can be immediately achieved, as opposed to liquid injection, in which powder flow must be slowly increased to prevent motor overload
- Reduces machine wear, as indicated by the extruder no longer experiencing the loud knocking noises indicative of screw deflection caused by uneven powder flow.

These observations are thought to be related to the two-stage wetting mechanism previously described, which causes the powder to become immediately isolated from the barrel wall by a layer of foam, at least until it is well wetted. The powder in this case is steadily saturated with the binder over a much larger area of contact than in direct liquid addition, which minimizes the binder's local concentration in the porous matter. The lubricating feature of foam granulation, in which the foam layer isolates the powders from the barrel wall until uniformly wetted, is an important point to be stressed for extrusion processing. The lubricity of conveyed solids affects both power consumption by the machinery as well as the exiting temperature of granules (2).

Comparing foam and conventional wet granulation

A study at pilot-scale flow rates (20–40 kg/h) compared foamed-binder addition and direct liquid-injection on granulation (6). A methylcellulose binder (Dow, Methocel A15 PLV) was used at two concentrations, 6% and 11% (w/w), relative to α-lactose monohydrate powder. Two screws were tested in the work to produce differing axial compression characteristics (which was mentioned previously as an important factor for granule growth inside the extruder) with changing flow rate: one with a single pair of mixing elements producing lower axial compression (LAC) and a second with two pairs in series to provide a more restrictive flow path and higher axial compression (HAC). Notable differences between the two methods of granulation are summarized in **Table 1**. The granule properties from the study showed that comparable sizes and intragranular porosity were achieved by either method, provided appropriate conditions were used. The reduced requirement for liquid in the process was a comparable finding to that found with high-shear batch mixers (15).

Conclusions

Wet granulation in twin-screw extrusion machinery has several key advantages over conventional methods, but to advance in acceptance for GMP production, its operations need to be better understood and challenges regarding process stability need to be solved. Continuous foam granulation is a new, robust technique that solves the process-surging issues that relate to poor powder wetting by conventional, liquid-addition methods. The high spreading tendency of foam in granulation, versus the immediate soaking nature of liquids, produces more uniformly wetted powders and increases the overall lubricity of the process, which benefits wear behavior of the machine and minimizes dissipative heating of the product. With comparable particle properties to conventional wet granulation, foam granulation gives formulators greater flexibility in achieving production goals.

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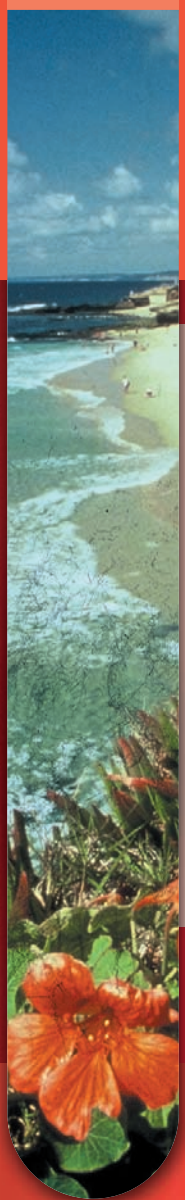

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The Role of Analytical Science in Implementing Quality by Design

Technical and Regulatory Aspects

Phil Nethercote, Graham Cook, Moheb Nasr, Siegfried Schmitt, Lucinda Buhse

The Parenteral Drug Association (PDA) organized a workshop aimed at identifying the role analytical science plays in supporting the implementation of quality-by-design (QbD) concepts and some of the challenges and opportunities QbD creates. The authors present topics discussed and conclusions that resulted from the PDA workshop.

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The recognition that the current pharmaceutical industry's manufacturing performance was not as state of the art as other industries has been a key driver behind the increasing adoption of quality-by-design (QbD) concepts. *The Gold Sheet* from January 2009 compares the operations performance of the pharmaceutical industry with other industries such as automotive, aerospace, computer, and consumer packaged goods and across a long list of measures, the pharmaceutical industry compares poorly.

Industry efforts to address these performance issues have focused on Six Sigma/Operational Excellence concepts and, since the issue of new International Conference on Harmonization (ICH) guidelines (i.e., ICH Q8, 9, 10, and 11), on the concept of quality by design. These initiatives have significant implications for pharmaceutical analysts. The desire to improve first-pass yield with zero defects has seen laboratories come under great scrutiny to ensure that all the methods they run work right first time, every time. To reduce inventories and lead times to those typically achieved in other industries, manufacturing planners must know with absolute confidence how long manufacturing and testing will take; rerunning a problem method is no longer an acceptable option. Zero-defect goals have also seen a focus on understanding and improving process capability (i.e., reducing the overall process variation relative to specification), and therefore, there is a much greater focus on truly understanding the variation contribution of the analytical method to the overall process variation.

QbD concepts described in ICH Q8, 9, 10, and 11 provide approaches that can help achieve the desired improvement in process performance (1–4). ICH Q8(R2) and 11 recognize the importance of effective process development in understanding the relationship between process variables and process performance. ICH Q9 describes how risk-based approaches can be used to determine which variables are crucial to control. ICH Q10 highlights the importance of effective processes for maintaining the control strategy through the lifecycle of the product.

A major focus of discussion and implementation of QbD has been on the concepts included in the ICH Q8 definition (i.e., product and process understanding and process control).

Understanding and control, however, cannot be achieved without a solid foundation of measurement or analytical science. During process development, analytical data are needed to provide the basis for process understanding. Control strategies based on this understanding are increasingly being developed based on recognition of the importance of identifying and controlling variation upstream rather than testing the end product. This control of variation has seen increasing use of process analytical testing (PAT) in preference to or in addition to end product testing, and with it, new technologies to be mastered by analytical scientists. QbD has also seen a focus on understanding and controlling attributes of excipients used in the manufacturing process, with increasing use of physical measurement technologies.

In addition to affecting what analytical scientists measure, the concepts of QbD, can also be used to enhance the robustness of the analytical methods themselves (5). One implication of such an approach is that it highlights the potential to re-examine the way that methods are developed and validated, in the same way that application of QbD to manufacturing processes has driven a revision in thinking of how process development and validation are performed (6, 7).

Taking advantage of the potential improvement opportunities through adoption of QbD concepts, however, does have some challenges. The ability to introduce improvements to analytical methods and to adopt new analytical technologies can be constrained, both through the need for industry to acquire new skill sets and through the challenges associated with making postapproval regulatory changes. These challenges are multiplied many times as a consequence of the global nature of the pharmaceutical business, with many stakeholders (e.g., regulators, pharmacopeias, consensus standards bodies) making harmonization of approaches particularly challenging.

What is measured

The introduction of QbD has challenged traditional thinking on pharmaceutical development and manufacturing. There has been a greater focus on developing science and risk-based control strategies based on product and process understanding over the more traditional approach of check-box compliance with reliance often on conventional end-product testing.

During process development, analysts are being challenged to provide more information on what process and material attributes are truly crucial to process performance. Greater emphasis on understanding the role the physical attributes of input materials play in the process has seen increasing adoption of advanced physical-properties measurement technologies. In-line measurement technologies coupled with multivariate

PDA workshop on analytical science and QbD

The Parenteral Drug Association (PDA) organized a workshop, held on Mar. 6–7, 2012, aimed at identifying the role analytical science plays in supporting the implementation of quality-by-design (QbD) concepts and some of the challenges and opportunities QbD creates. The workshop provided a forum for regulated industry and key stakeholders from regulatory authorities (FDA, European Medicines Agency, and the UK's Medicines and Healthcare products Regulatory Agency) and pharmacopeias (European Pharmacopoeia, British Pharmacopoeia) to explore the implications of QbD on analytical science and to assess the future direction and implementation challenges. Diverse representation including analytical scientists and regulatory affairs staff involved in development and manufacturing engaged in an open exchange of ideas during the three topic breakout sessions and the plenary panel discussions conducted over two days. Challenges and issues were identified for topics covering:

- How the critical product and process attributes that are measured change with a QbD approach
- The implications of QbD on specification limits and sampling
- How QbD concepts can be applied to analytical methods development and how this affects method validation approaches
- How implementation of improved and innovative methodologies can be facilitated
- The challenges of global alignment of standards.

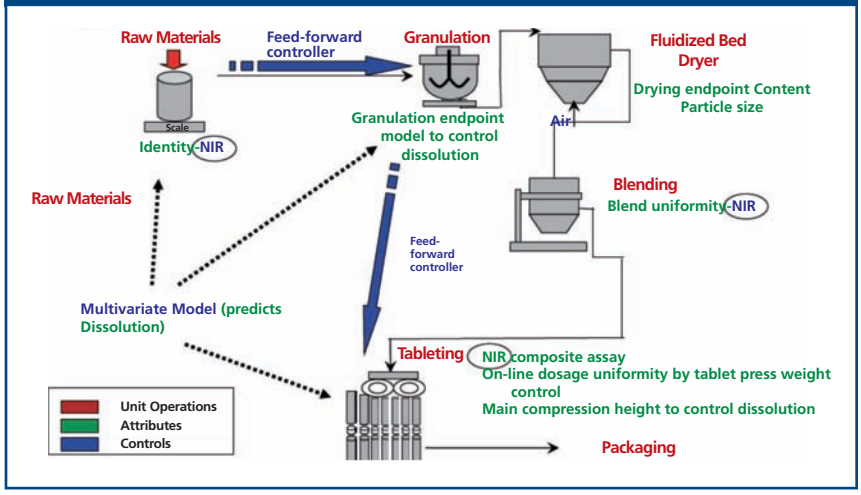
The workshop participants suggested a number of potential actions that might help address these challenges including:

- Agreeing on unique, unambiguous, and well-defined terminology
- Reviewing existing International Conference on Harmonization (ICH) guidelines, and developing a white paper on proposed revisions and potential new guidelines, if any, that would support and enhance the role of analytical methods in QbD
- Exploring, during the forthcoming revision to the EU variations guidance, how the Post-Approval Change Management Concept might be used to facilitate continuous improvement and innovation of analytical methodology
- Establishing mechanisms to ensure global alignment of new pharmacopoeial\ regulatory texts and guidance in this area (e.g., large sample size guidance and method validation)
- Developing case studies and aligned terminology to ensure consistent understanding of how QbD can be applied to analytical methods and further explore how analytical target profile (ATP) can be presented in regulatory submissions
- Holding further workshops in the US and in Asia focusing on case studies in order to support global alignment of concepts.

At the PDA workshop, Bernadette Doyle, vice-president, technical, GMS within GSK, presented an industry view on the ideal future state as:

- Every test performed adds real value in assuring patient safety, product quality, and process robustness
- Analytical processes (e.g., method development, validation, transfer, change management, issue resolution) are fit for purpose and underpinned by a science- and risk-based approach
- Analytical methods are robust, continuously improved across the product lifecycle, and reflect best-in-class technology
- Knowledge is maintained and refreshed to support future learning and analyst competency
- Continuous improvement of analytical methods is not constrained by regulatory barriers
- There are clear and appropriately harmonized standards (or mutual acceptance) of analytical measurement activities across all markets.

Figure 1: Manufacturing process where the contols are in-process.



statistical analysis techniques are being used to provide greater understanding of what is actually happening during each of the process steps.

Risk assessments of processes are increasingly being used to evaluate the need or value of a particular measurement within the control strategy to reduce the risk to product quality. A measurement, for example, may be applied to in-process quality control, or perhaps as an approach to improve detectability of a failure mode examined in a failure mode and effects analysis (FMEA).

The effectiveness of in-process control in assuring product quality has been recognized (8). A number of pharmaceutical companies have developed manufacturing processes where the controls are in process and a control strategy similar to **Figure 1** is used.

A PAT-enabled process allows increased sampling of the process material to be performed, thereby increasing the information about the process. The increased sampling can, however, increase the risk of failing a zero-tolerance specification found in a uniformity of dosage units test, for example. Pharmacopoeial authorities have recognized this disincentive to the adoption of large sample sizes and responded by proposing alternative approaches (9).

PAT-enabled processes may also present challenges to the traditional paradigm of batch release based on end-product testing and specifications. The PAT-enabled process may evaluate different attributes or end-points, use multivariate statistical analysis of process data, and also require an understanding of the distribution of data, all of which may affect the determination of appropriate acceptance criteria.

The implications of these changes include tools that support process understanding (e.g., granule porosity), new technologies and skill sets (e.g., near infrared, imaging, statistics), and new behaviors (e.g., risk assessment vs. check box compliance).

Application of QbD concepts to analytical methods

The concepts of QbD as articulated in ICH Q8, Q9, Q10, and Q11 are aimed at improving the robustness of pharmaceutical manufacturing processes and enabling continual improvement. They focus on taking a systematic structured approach to identifying process variables and how these variables relate to the desired process outputs and pharmaceutical products. Such enhanced understanding combined with application of formal risk-assessment processes are used to identify the critical attributes and parameters that should be controlled to assure product quality. Lifecycle knowledge and change-management processes then ensure that control strategies remain effective through the lifecycle. By considering an analytical method as simply a process, it is possible to apply these same concepts to provide enhanced confidence of the robustness of analytical methods. As mentioned above, this increased focus on robust methods is becoming an increasing area of concern for analytical scientists as non-robust methods undermine the ability to plan manufacturing and related quality assurance activities with confidence. Increased regulatory scrutiny on out-of-specification (OOS) investigations and effective root cause analysis of these is another key driver for ensuring method variables are well understood and controlled.

In 2010, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) jointly issued a white paper aimed at stimulating discussion between industry, regulators, and pharmacopeias on the potential benefits and implications of applying QbD concepts to analytical methods (5). A number of companies are now adopting this approach as they are seeing benefits in terms of increased method understanding, robustness, and ruggedness. During a Parenteral Drug Association (PDA) workshop, held Mar. 6–7, 2012 in Liverpool, UK, it was acknowledged that there are no regulatory barriers to adoption of a QbD approach for analytical method development and validation; however, it was also recognized that thinking may need to change about approaches to analytical method validation (10).

A lifecycle approach to method validation has been proposed (11) and indeed some of the concepts behind application of QbD to method development and validation have started to be promoted, particularly by the United States Pharmacopeia (USP) (12, 13) and through ASTM guidance on validation of PAT methods (14). Recently, USP has established an expert panel to explore whether the chapters on method validation, method verification, and transfer of analytical procedures may become amalgamated into a single chapter describing how methods are assured to be fit for purpose through their lifecycle. Sample replication levels, criteria for agreement between replicates, system performance requirements, repeat testing required for OOS and equivalence testing criteria should all ultimately be able to be linked back to an understanding of the methods performance and the targets for accuracy and precision that are required.

As noted above, a common understanding between pharmacopeias, regulatory agencies, consensus standards organizations, and industry on the description, application and interpretation of QbD concepts as applied to analytical methods is essential if they are to be more widely adopted. The PDA workshop recognized that alignment of understanding was key and that better clarity was desired on some of the terminology and concepts being used (e.g., method operable design region [MODR] vs. analytical design space [ADS], analytical target profile [ATP] vs. procedure performance acceptance criteria [PPACs]), and participants proposed the development of case studies to better illustrate the concepts. A key point that arose during the workshop that needs further discussion is whether a method is validated to meet a target performance (which is defined from the specification limits) or whether the specification limits are set based on the method capability.

Innovation and improvement

The ability to innovate and improve is crucial, not only to ensure the most up-to-date technologies are used to ensure patient safety, but also to improve efficiency and eliminate waste. There have been a number of recent examples of incidents where contamination of drugs has resulted in serious patient harm (e.g., heparin, melamine). These incidents have led to the development and introduction of modern analytical technologies (e.g., nuclear magnetic resonance [NMR]) to help mitigate risks of future occurrences. The pharmaceutical industry has not been quick to adopt new measurement technologies for a variety of reasons such as the significant costs, potential regulatory risk, and resources associated with changing the registered details globally. At the PDA workshop, an example was shown that illustrated the significant cost that a pharmaceutical manufacturer may be faced with attempting to introduce improvements to analytical methodology when products are registered in many global markets. Reducing the barriers to innovation and improvement through better regulation has been a focus of governments through programs such as the UKs Better Regulation of Medicines Initiative (BROMI) or the Executive Order 13563—Improving Regulation and Regulatory Review in the US.

There are examples from the pharmaceutical industry where flexibility to use any appropriate method is allowed (e.g., FDA's melamine guidance) (15) which states "alternative method or methods can also be qualified for use in screening components for the presence of melamine" and defines the performance required as, "The test method used should be suitable for detecting melamine contamination in at-risk components down to at least 2.5 parts per million (ppm)," or FDA'S Heparin Guidance (16) that again allows alternative methods to be used. Recent proposed changes to the FDA guidance on sterility testing are "intended to provide manufacturers of biological products greater flexibility and to encourage use of the most appropriate and state-of-the-art test methods for assuring the safety of biological products" (17).

The concepts of comparability protocols/postapproval change management protocols introduced in October 2012 in the US and in Europe may provide a mechanism of facilitating easier postapproval changes. Again, as previously stated, from an industry perspective it is crucial that there be alignment in thinking in this area.

Global alignment of stakeholders

As highlighted already, it is key for an industry that manufactures and markets globally to have a regulatory framework that also operates globally (aligned and harmonized). In the field of analytical science, the regulatory framework is defined by a number of stakeholders—the regulatory authorities, the pharmacopeias, and other standard setting bodies such as ISO and ASTM, which may be recognized by the regulatory authorities. With the changes associated with the introduction of QbD, it is important that the thinking and concepts are aligned across these different bodies. The development and publication of ICH Q8, 9, 10, and 11 have played a significant role in motivating alignment among the ICH regions; however, not all the thinking in this area is integrated. It is, however, recognized that the European Pharmacopoeia has already been offering flexibility including the use of alternative approaches for a number of years, which is expressed in particular in the *Ph.Eur.* (General Notices section 1.1). Moreover, the European Pharmacopoeia has been playing a leading role in developing thinking on the implications of large sample sizes (9). The USP has been promoting the concept of performance-based monographs and has issued examples of these in a new USP Medicines Compendium as well as a general chapter on how to define performance requirements for methods. USP has also recently established an expert panel that is looking to revise its guidance on method validation and verification. ASTM has been developing guidance on how PAT methods should be validated, while the EMA has issued new draft guidance on use of NIR (18). FDA is promoting thinking on the use of confidence intervals for batch release decisions with reference to ASTM guidance on this topic (19).

Ensuring global alignment is an extremely difficult goal; however, from an industry perspective it is the key barrier to innovation and effective implementation of QbD. To advance these concepts, more must be done in this area. It is encouraging to see that pharmacopoeia authorities have agreed to discuss global good pharmacopoeial practices under the auspices of the World Health Organization (WHO).

Target state

The ultimate goal of QbD has been summarized in a statement from Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at FDA, who suggested during a ISPE and AAPS-sponsored CMC workshop on Oct. 5, 2005, that a mutual goal of industry, society, and regulators is "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight." To achieve this goal, it is crucial that we move from a checkbox, compliance-focused culture to one that is founded on a science- and risk-based approach to assure quality and compliance.

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Outsourcing Nontraditional Protein Expression Systems

Eric Langer

Growth is seen in outsourcing of insect- and plant-cell-based bioproduction expression systems.

The biopharmaceutical industry continues to increase outsourcing less common, more complex processes as companies seek strategic advantage by leveraging external resources. Until recently, outsourcing has focused primarily on traditional expression systems (mammalian and microbial) versus less common systems (e.g., yeast, plant cell, and insect cell) more likely to be retained in-house.

This year, there are signs that outsourcing of plant- and insect-cell culture-based processes are beginning to expand. Preliminary data from BioPlan Associates' *10th Annual Report and Survey of Biopharmaceutical Manufacturers* indicate that only 50% of plant-cell users are performing this operation fully in-house, with the other half outsourcing some elements of bioprocessing to some degree. The data represent a shift from prior years, when up to 90% of the industry kept their processes fully in-house.

The BioPlan data for insect-cell systems shows a similar trend. In past years, between 65% and 100% of respondents did all their insect-based production in-house, but BioPlan's preliminary data from 2013 show a reduction to 60% of respondents doing all insect-cell-based production in house; this is the lowest point in more than six years. For plant-cell and insect-cell systems, the smaller number of facilities using these systems and the fact that the data still being preliminary make it too soon to declare a definitive shift, but it is interesting to see that the trends projected by some industry analysts are reflected in the preliminary findings. Meanwhile, the proportion of respondents outsourcing traditional expression systems remains relatively steady as follows (2013 results are preliminary data):

- *Mammalian cell-culture systems*: In 2013, 50% of respondents (47% in 2012 and 45% in 2011) indicated that they outsourced no production while 31.6% (47% in 2012, 44.6% in 2011, 30.3% in 2010, and 29% in 2009) outsourced up to half of production.
- *Microbial fermentation:* In 2013, 45% (50% in 2012 and 43.8% in 2011) of respondent outsourced no production. Thirty-five percent (44.% in 2012 and 41.6% in 2011) outsourced up to half of production, and 20% outsourced more than half.
- *Yeast systems*: In 2013, 66.7% of respondents (62.5% in 2012, and 59.1% in 2011) outsourced no production; in 2013, 22.2% of respondents (31.3% in 2012, 27.2% in 2011, 32.1% in 2010, and 14% in 2009) outsourced up to half of production.
- *Plant-cell systems*: 50% outsourced no production in 2013 (89% in 2012, 58% in 2011, and 75% in 2010).
- *Insect-cell systems*: 60% outsourced no production in 2013 (83% in 2012, 65% in 2011, 100% in 2010, and 82% in 2009).

Future outsourcing

When the BioPlan survey separately asked respondents about the percentage of their production that they expect to outsource in five years (i.e., by 2018), similar trends hold true. Future outsourcing of plant- and insect-cell systems appears to be rising while outsourcing of traditional systems remains steady, suggesting a relatively stable production environment. The preliminary data from 2013 show:

- *Mammalian cell-culture systems*: 62.5% of respondents in 2013 (58.2% in 2012 and 63.5% in 2011) indicated they expect to outsource at least some of their production in the next five years.
- *Microbial fermentation*: In 2013, 68.2% of respondents (72.2% in 2012 and 59.6% in 2011) plan to outsource some production by 2018.
- *Yeast systems*: 40% of respondents in 2013 (45% in 2012 and 52.2% in 2011) believe that at least some of their production will be outsourced in the next five years.
- *Insect-cell systems:* 42.9% of respondents in 2013 (26.7% in 2012) plan to outsource some production by 2018.
- *Plant-cells systems*: 40% of respondents in 2013 (25% in 2012) expect to outsource some production in the next five years.

Capacity utilization trends

Although outsourcing of traditional expression systems has remained fairly steady in BioPlan's preliminary data, capacity utilization may be trending upward after several years of decline. Capacity utilization is important for ensuring productivity and cost-effective operations. Lower utilization equates to more idle capacity. A certain amount of flexible capacity is needed to ensure availability during stress operations. Also, CMOs require open capacity to ensure they are not turning away potential clients. Conversely, too little capacity can lead to production and delivery problems. Ten years ago, capacity utilization was a more prominent issue. Today, increased yield of titers, improved bioproduction modeling, the use of disposables, and better planning have lifted most capacity problems.

Manufacturers, however, continue to work toward optimized upstream

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and downstream process operations. In upstream bioprocessing, mammalian cell-culture capacity in 2013 is averaging 65.4% of total capacity, which would be its highest level since 2006, according to BioPlan's preliminary data. Capacity use has stabilized at roughly 62% during the past six years after declining from 76.4% in 2004. Meanwhile, the rebound is even greater for microbial fermentation. After decreasing steadily from 71% in 2004 to 49.5% in 2012, capacity utilization appears to have increased to 62% this year. For yeast culture, the initial data showing 48.4% capacity utilization represent an uptick from a 2012 level of 35.7%, but is more in keeping with prior years, which ranged from 44.9% to 46.8% between 2006 and 2011. Capacity utilization for plant- and insect-cell systems remains steady comparative to 2012, but noting again the potential for "noisy" data due to the small number of respondents using these systems.

For essentially all expression systems, there appears to be underutilized capacity, which is preferable for companies when compared to a shortage of capacity. Despite utilization percentages having decreased in recent years, new capacity and higher yields were established during this period, so overall biomanufacturing levels (i.e., output) have risen considerably.

Conclusion

Despite steady utilization rates in insect- and plant-cell expression systems, outsourcing appears to be rising. For traditional mammalian and microbial expression systems, capacity utilization rates are trending upward while outsourcing has remained flatter. On the surface, capacity utilization and outsourcing would appear to be interconnected—when capacity is scarce, outsourcing becomes an option. For many bioprocessing technologies, however, selection factors may be more associated with the availability of technical competence among outsourcing suppliers and CMOs rather than simply access to available production capacity. **PT**

Quality by Design – *contin. from page 77*

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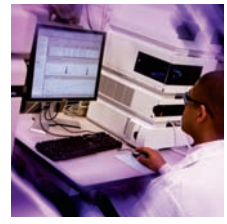

Bioanalytical analysis

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*

Crystallization services

Cambridge Major Laboratories's Netherlands-based Center of Excellence for Crystallization and Solid State Chemistry offers crystallization to obtain stable solids for purification or isolation. Additional services include: material characterization, solubility determination for production solvents and buffer solutions, salt selection, and crystallization process development to combine optimal synthesis conditions with crystal-habit optimization. **Cambridge Major Laboratories,** *Germantown, WI • www.c-mlabs.com • tel. 262.251.5044*

OUTSOURCING & CONSULTING SERVICES

Pharmaceutical services

WellSpring Pharmaceutical is a full-service provider of clinical and commercial manufacturing and packaging, blinding, method development, analytical testing, and distribution services. Highly qualified managers and technical professionals work at the company's 100,000-ft² facility to ensure that clients' clinical and commercial products meet high standards. **WellSpring Pharmaceutical Canada,** *Oakville, Canada • www.wpcoutsourcing.com • tel. 866.337.4500*

Parenteral Contract Manufacturing Service of Hospira

Contract-manufacturing services

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

Product-development guidance

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

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*

LABORATORY EQUIPMENT & SUPPLIES

Trace-metals analysis

The Discover SP-D System from CEM performs microwave-assisted closed vessel digestions for trace metals analysis in only 10 minutes, including cool down. Automation options are available and the system can run unattended. The Discover SP-D is compact and offers temperature and pressure control, easy-to-use vessels, and documentable results. The system also includes a guide for implementing USP Chapters 232, 233, and 2232. **CEM Corporation,** *Matthews, NC • www.cem.com • tel. 800.726.3331*

Laser-diffraction particle-size analyzer

Shimadzu's SALD-2300 provides continuous measurement in real time, at minimum one-second intervals. Its measurement range spans particle sizes from 17 nm to 2,500 µm, and users can select various sample amounts depending on measurement objectives. A measurement assist function reduces operational errors while powerful self-diagnostics ensure reliable analysis. **Shimadzu Scientific Instruments,** *Columbia, MD • www.ssi.shimadzu.com • tel. 800.477.1227*

LABORATORY EQUIPMENT & SUPPLIES

Laboratory and processes catalog

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

Spectroscopy and imaging systems

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

Chromatography analytical system

Waters's Acquity Ultra Performance Convergence Chromatography (UPC^2) System is intended for reversed-phase liquid and gas chromatography separations, and offers a replacement option for normal-phase chromatography applications. The Acquity UPC^2 system is especially designed for tough-to-analyze compounds, including hydrophobic and chiral compounds, lipids, thermally-labile samples, and polymers. **Waters,** *Milford, MA • www.waters.com • tel. 508.478.2000*

LABORATORY EQUIPMENT & SUPPLIES

Manufacturing operations analyzer

ABB's TALYS ASP500 series analyzer is a fiber-optics based industrial FT-NIR analyzer designed for in-line monitoring and control of batch or continuous processes. Its seamless installation enables reactor profiling, real-time determination of process end-point, cycle-time reduction, process characterization, and early troubleshooting. The analyzer features an embedded processor and is built for long maintenance free operations in manufacturing environment. **ABB,** *Quebec City, Canada • www.abb.com/analytical • tel. 418.877.2944*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

Chemicals and laboratory products

Spectrum Chemicals & Laboratory Products announces two new life sciences reagent distribution agreements with bioWorld and Accumedia. Spectrum is now the premier distributor of bioWorld's 4000+ affinity chromatography, molecular biology, cell culture, and microbiology products and Accumedia's complete line of dehydrated culture media. All products are available online. **Spectrum Chemicals & Laboratory Products,** *New Brunswick, NJ • www.spectrumchemical.com • tel. 800.772.8786*

Inorganic salts

Jost Chemical manufactures over 350 high-purity inorganic salts. The company's FDA-registered site in St. Louis, Missouri, totals 190,000 ft^2 and operates under bulk pharmaceutical cGMPs. Jost is a global supplier of chemical salts that meet USP/EP/BP/JP/ACS and multicompendia requirements. Jost's products are BSE/TSE free and allergen free, and its selection of products includes carbonates, nitrates, phosphates, and sulfates. **Jost Chemical,** *St. Louis, MO • www.jostchemical.com • tel. 314.428.4300*

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The Ceolus KG-1000 product is Asahi Kasei's most highly compactible microcrystalline cellulose (MCC). Only a small amount (as little as 5–10% in some cases) in a formula will provide the desired tablet hardness. The company also offers the Ceolus KG-802 and UF-711 ingredients, and additional highly compactible MCC grades with different properties to solve various tablet-hardness problems. **AsahiKASEI America,** *New York, NY • www.ceolus.com • tel. 212.371.9900*

Alpha-lactose-monohydrate

FlowLac 90 is a spray-dried alpha-lactose-monohydrate that helps enable virtually dust-free production. The excipient has outstanding compaction properties and a fast disintegration profile. Its spherical particles and porous surface provide excellent flowability and high content uniformity. FlowLac 90 is appropriate for low- and high-dosage direct-compression formulations. **MEGGLE Group Wasserburg,** *Wasserburg, Germany • www.meggle-pharma.com • tel. +49 0 80 71 73 4 76*

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Drug-storage system

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

EQUIPMENT & SUPPLIES

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Adhering to ICH Q7 for GMPs

David Elder, vice-president, technical at PAREXEL, discusses FDA's requirements for API manufacturers in regards to ICH Q7.

Q. How closely does FDA expect API manufacturers to adhere to ICH Q7 for GMPs?

A. ICH Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, like its ICH Q1–Q11 siblings, was developed within the designated ICH Expert Working Group and was subject to consultation by the regulatory parties, in accordance with the ICH process (1). In November 2000, ICH Q7 was endorsed by the ICH Steering Committee and subsequently adopted by the participating ICH regulatory bodies of the European Union, Japan, and the United States. It, therefore, has international adoption and acceptance. The overall ICH process is, in my opinion, the best example of successful international harmonization efforts, creating a foundation of common standards upon which meaningful leveraging opportunities may be built.

ICH Q7 itself provides guidance regarding cGMPs for the manufacturing of APIs under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess. Legally, FDA considers ICH Q7 to be the equivalent of "guidance." FDA guidance documents are quite helpful and typically explain the agency's interpretation of laws and regulations, often describing acceptable means and methods that would comply with the law and that may be considered best practices. Although guidance documents are not legally binding, following them is highly recommended. FDA cannot enforce guidance nor will it specifically cite departures from guidance in regulatory communication. The agency enforces the law and properly promulgated regulations that have the force and effect of law. How then is ICH Q7 used by FDA in the regulation of API manufacturers?

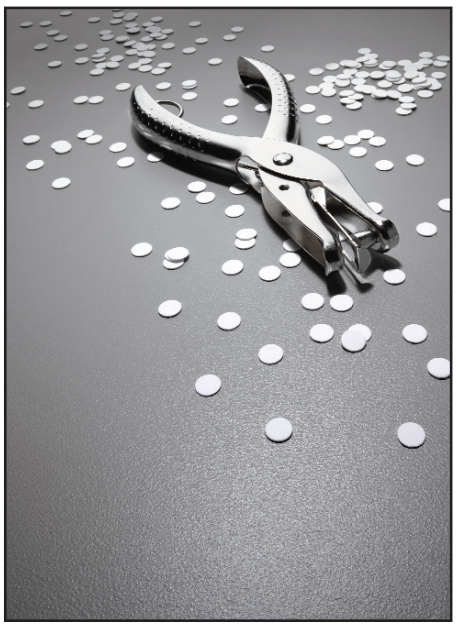
The Federal Food, Drug and Cosmetic Act Section 501 (21 USC 351) states that a drug (whether the drug is a finished pharmaceutical or a component of a finished pharmaceutical) is considered adulterated if "…the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice…"(2). For finished pharmaceuticals, the cGMP requirements are clear—the agency promulgated cGMP regulations for finished pharmaceuticals in 21 *CFR* 210/211 (3).

The agency has not established cGMP regulations for APIs. Nevertheless, APIs must still meet the provisions of the law and be manufactured in conformance with cGMP. But without regulations, what is considered to be cGMP for an API? The answer, for all practical purposes, is ICH Q7 is considered to be cGMP for an API. Closely following its provisions will not only help ensure your APIs are safe, pure, and potent, but following its provisions will also help ensure your APIs are not considered to be cGMP-adulterated.

References

1. ICH, Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (November 2000).
2. Federal Food, Drug and Cosmetic Act Section 501 (21 USC 351).
3. 21 *CFR* 210/211. **PT**

Ad Index



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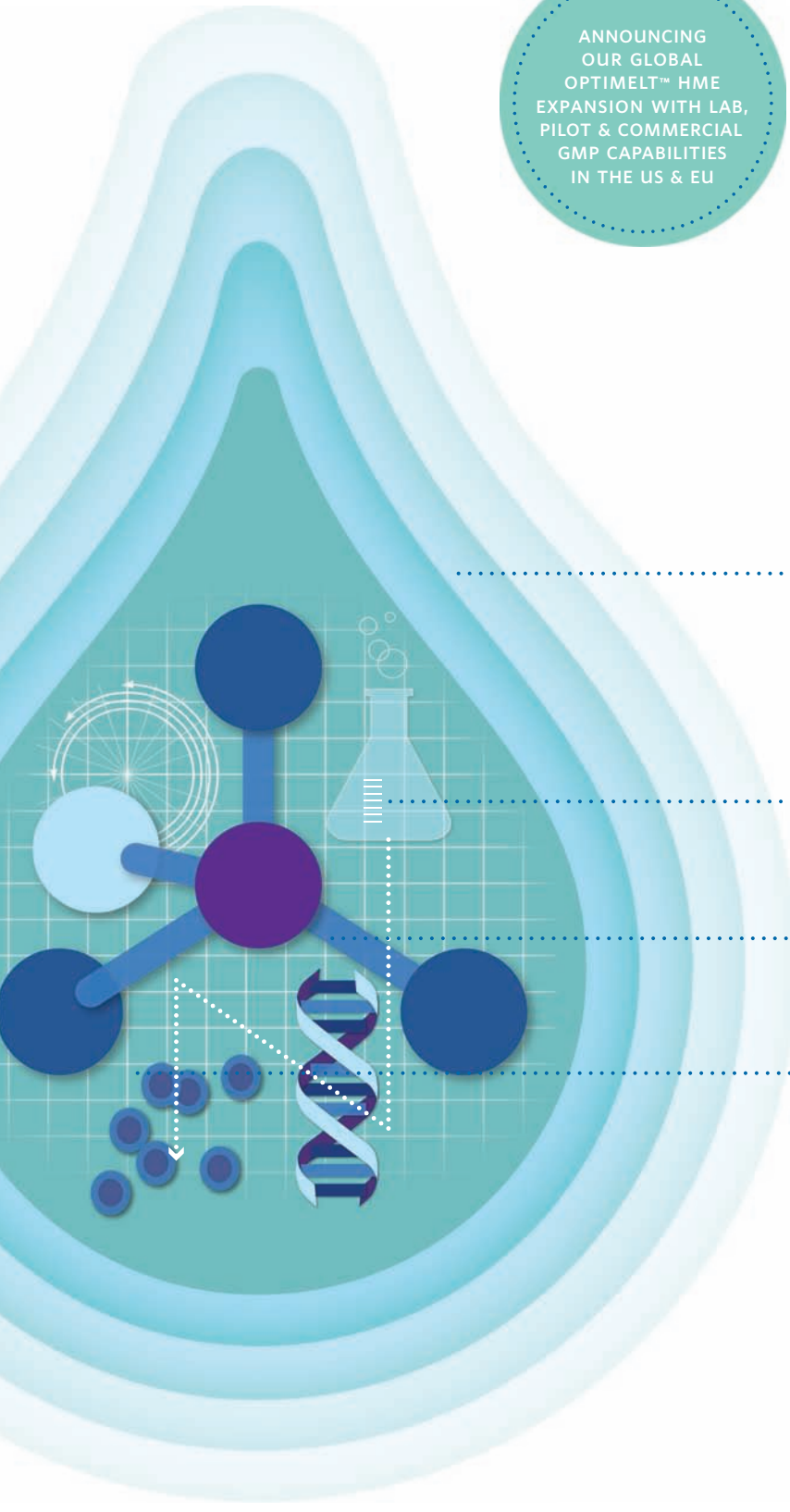

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