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Contributing Editors
• Jill Wechsler, jwechsler@advanstar.com
• Jim Miller, jim@pharmsource.com
• Hallie Forcinio, editorial@jcs.com
• Susan J. Schniepp, sue.schniepp@mac.com
• and Eric Langer, info@pharmaassociates.com

Correspondents: Hellen Berger (Latin/South America, hellen.berger@terra.com.br)
• Sean Milmo (Europe, smilmo@btconnect.com)
• Jane Wan (Asia, wanjane@live.com.sg)

485 Route One South, Building F, First Floor, Illinon, NJ 08830, USA
Tel: 732.596.0276, Fax: 732.647.1235, PharmTech.com

Pharmaceutical Technology’s eNewsletter Team:
• RPeters, Editor Rita Peters, rpeters@advanstar.com
• Executive Editor, Patricia Van Arnum, pvanarnum@advanstar.com
• Managing Editor, Susan Haigney, shaigney@advanstar.com
• Scientific Editor, Adeline Siew, PhD, asiew@advanstar.com
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Henz Ducker, PhD
Professor Emeritus, Pharmaceutical Institute, University of Bern

Scott Sutton, PhD
Microbiology Network

Contributing Editors
• JPeters, Editor Chris Allen, jtpeters@advanstar.com
• Sourcing and Management, Editor Patricia Van Arnum, pvanarnum@advanstar.com
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Pathway to Publication

Rita Peters

Wanted: Article contributions on drug and process development topics.

One of the most frequent questions I receive as a publication editor is: How do I get my article published? Here is the answer to that question and more.

Pharmaceutical Technology (and its sister publication Pharmaceutical Technology Europe) publishes peer-reviewed technical articles and expert analyses for scientists, engineers, and managers engaged in process development, manufacturing, formulation and drug delivery, API synthesis, analytical technology, packaging, IT, outsourcing, and regulatory compliance.

Readers are PhD-level scientists, senior-level scientists, or senior production professionals specifically involved in formulation development, process development, and manufacturing of active pharmaceutical ingredients and finished drug-products; drug-delivery technologies; analytical methods development and testing; quality assurance/quality control and validation; and advances in pharmaceutical equipment, machinery, instrumentation, facility design and plant operations.

Peer-reviewed papers

Manuscripts accepted for peer review are published simultaneously in both Pharmaceutical Technology and Pharmaceutical Technology Europe. Papers are also posted on www.PharmTech.com. Peer review is double blind, where the identity of reviewers is unknown to authors and vice versa. Articles submitted for peer review may fall into four main categories: standard data-driven, novel research paper; topical literature or patent review; technical case studies/technical application notes; and science-based opinion papers.

Technical articles

Technical articles and analyses, published in monthly issues and supplements, should be objective and technically relevant. An article can be a technical case study, demonstrating a problem resolution with related technical data and analysis; an explanation of a new or enhanced technology and related applications; an explanation of new compendial or regulatory standards; a topical literature review; a review of industry developments in a given area; or a review of regulatory developments and compendial requirements and related analysis.

The topics

The editors welcome subjects relevant to formulation development, process development, and manufacturing of APIs (both small molecule and large molecules) and finished drug-products (solid dosage, semisolid, liquids, parenterals drugs, topical drugs). The potential topics include drug-delivery technologies; drug substance manufacturing, scale-up, and process development; analytical methods development and testing; compliance, quality assurance, quality control, and validation; facility design, plant operation, engineering, process control and automation; quality by design, continuous processing; and emerging manufacturing approaches.

The authors

Pharmaceutical Technology seeks contributions from all participants in the drug development community. Manuscripts are reviewed with the understanding that they have not been published previously, are not ghostwritten, and are not under consideration for publication elsewhere, including on the Internet.

Submission deadlines

Peer-reviewed submissions are reviewed on a rolling basis. Depending on the manuscript, peer-reviewed articles usually take about one to two months for review, revision, and acceptance by the editors. Once accepted, an article is published within four to eight months.

Technical, non peer-reviewed articles fit topics on the annual editorial calendar and are typically assigned three to five months before the issue is published. If you would like to contribute an article, send an outline or abstract proposal to Pharmaceutical Technology. If your topic is accepted, an editor will assign you an official deadline, approximately six weeks before the publication date.

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HITTING THE HEADLINES

Big Biotech Outpaces Big Pharma
Big Biotech companies are demonstrating they are better positioned than their pharmaceutical industry counterparts to meet changing demands, outpacing Big Pharma in terms of growth of sales, income, investment in R&D, and market cap during the past three years, according to an analysis by Burrill & Company. Big Biotech enjoyed a 57% increase in market cap for the three years ending Dec. 31, 2012, compared to a 17.4% increase for Big Pharma during the same period. PharmTech.com/burrill

Amgen Pays $25 Million for Violations
Amgen Inc. has agreed to pay the United States $24.9 million to settle allegations that it violated the False Claims Act. The settlement resolves allegations that Amgen paid kickbacks to long-term care pharmacy providers in return for implementing therapeutic interchange programs that were designed to switch Medicare and Medicaid beneficiaries from a competitor drug to Amgen’s Aranesp. The government alleged that Amgen distributed materials to consultant pharmacists and nursing home staff encouraging the use of Aranesp for patients who did not have anemia associated with chronic renal failure. PharmTech.com/amgen

FDA: No Generics to Original OxyContin
FDA approved updated labeling for Purdue Pharma L.P.’s reformulated OxyContin tablets, but also determined that it will not approve generic versions of the original OxyContin. The new labeling indicates that Purdue Pharma’s reformulation has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route. However, the agency ruled that because original OxyContin provides the same therapeutic benefits as reformulated OxyContin, but poses an increased potential for certain types of abuse, the benefits of original OxyContin no longer outweigh its risks. Original OxyContin was withdrawn from sale and the agency will not accept or approve any abbreviated new drug applications that rely upon the approval of original OxyContin. PharmTech.com/oxycontin

FDA Requests Almost $5 Billion for 2014 Budget
FDA is requesting $4.7 billion as part of the President’s fiscal year (FY) 2014 budget including a $15-million decrease in budget authority for human drug, biologics, and medical device programs. The FDA budget request includes $179 million more than FY 2012 to modernize regulatory science and promote medical product innovation. It also includes more than $10 million above the 2012 budget for food and drug safety inspections of products and ingredients manufactured in China. PharmTech.com/2014budget

READERS THINK THAT...

How do you think the reputation of the pharmaceutical industry has changed in recent years?

- Improved: 25%
- Stayed the same: 45%
- Declined: 25%

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ON THE BLOG

“A scientist working for Aptuit has been jailed three months for falsifying preclinical safety data on experimental anticancer drugs due for clinical evaluation.”
Adeline Siew

“The Obama administration’s budget plan for fiscal year 2014 apparently assumes that the pharmaceutical industry can support Medicare and other health programs through changes in drug coverage and payments. It also relies on industry fees to keep FDA up and running.”
Jill Wechsler

“As the availability of late-stage development opportunities shrink and the landscape becomes more competitive, Big Pharma is turning to early-stage partnerships with academia and early-stage biopharmaceutical companies.”
Rita Peters

“The Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom unveiled its 2013–2018 corporate plan, announcing its aims to be a leading regulator on the world stage in supporting science and research.”
Adeline Siew

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EVENTS

2013 PDA/FDA Glass Packaging Conference
May 15–16, 2013
Bethesda, MD USA

World Biotechnology Congress 2013
June 3–6, 2013
Boston, MA USA

Pharma Outsourcing & Procurement Summit 2013
June 5–6, 2013
Berlin, Germany

8th Annual Global Pharma Manufacturing Summit 2013
June 27–28, 2013
Boston, MA USA

Pharma Trials World Korea 2013
July 8–11, 2013
South Korea

INDUSTRY NEWS

• Oval Medical Technologies, an autoinjector company based in Cambridge, UK, reported that a variety of highly viscous solutions have been successfully delivered through a 25-gauge thin-wall needle, in less than 7 seconds, using its innovative autoinjector. Viscosity is a challenge for many biopharmaceutical formulators given that a number of biologics are highly viscous.

• Cipla has launched the first biosimilar of etanercept in India for the treatment of rheumatoid disorders. The product will be marketed under the brand name Etacept. The launch of Etacept marks Cipla’s entry into the biologics market, offering a low-cost alternative to Pfizer and Amgen’s rheumatic disorder blockbuster Enbrel in India. Etacept contains the biologic etanercept, which is produced by recombinant DNA technology. The product, manufactured by China’s Shanghai CP Guojian Pharmaceutical Co. Ltd., is available as a lyophilized powder for subcutaneous injection.

• GE Healthcare and iBio Inc. have signed a contract under which GE Healthcare will design a new plant-based multipurpose manufacturing facility for Bio-Manguinhos/Fiocruz, a manufacturer of immunobiologicals based in Brazil. The alliance combines iBio’s iBioLaunch with GE Healthcare’s capabilities in process design and biopharmaceutical and vaccine manufacturing technologies. The iBioLaunch platform is a proprietary technology for the development and production of biologics using transient gene expression in unmodified green plants.

• In mid-April, Merck announced that it opened a facility in Hangzhou, China to package Merck medicines for China and the Asia Pacific region. The facility, a nearly $120-million investment by Merck, is located in the Hangzhou Economic and Technology Area (HEDA). The new 75,000-m² facility is capable of holding up to 16 high-speed lines to package pharmaceutical tablets and sterile Merck medicines that are used to manage diabetes, cardiovascular, infectious, respiratory, and bone diseases. The HEDA facility received a cGMP certification in January 2013.

• Thermo Fisher Scientific will acquire Life Technologies for approximately $13.6 billion, plus the assumption of net debt at close, which was $2.2 billion as of year-end 2012. The deal is expected to close in early 2014, pending Life Technologies’ shareholder approval and regulatory approvals. Life Technologies focuses on research consumables, genetic analysis, and applied sciences. Thermo Fisher Scientific develops and markets analytical technologies and specialty diagnostics.
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Editors’ Picks of Pharmaceutical Science & Technology Innovations

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The Accelrys Process Management and Compliance Suite has been expanded with the addition of the Accelrys Laboratory Information Management System (LIMS). This system uses a process-driven approach, which focuses on laboratory, quality-control, and manufacturing processes, in contrast to the sample-driven approach used by traditional LIMS. This process-driven approach enables organizations to achieve repeatability and consistency of procedures, automatically qualify operational changes, and maintain a lower total cost of ownership. The Accelrys LIMS integrates with Accelrys Electronic Laboratory Notebook (ELN), Accelrys Laboratory Execution System (LES), Accelrys Electronic Batch Records (EBR), Accelrys Discoverant process management informatics, and the Accelrys Enterprise Platform (AEP) for data exchange to provide an end-to-end informatics system that makes data accessible across an organization.

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Software streamlines compliance and quality management
GXPI has unveiled X-forms as the latest extension to its electronic document management platform (EDM) X-docs. The X-forms interface is designed to manage, track, and resolve quality issues for the life-sciences industry. The product comes complete with functionality to facilitate several quality processes, including change control, CAPA and deviation management, audit management, and other client-driven, quality process-related configurations. The X-docs platform was developed to streamline compliance processes to deliver both ergonomic functionality and long-term cost savings. Following installation to X-docs, X-forms can then be tailored to meet a range of specific business processes in the quality related space, and also provide the ability to add further modules as clients grow, all on the same, familiar platform.

GXPI
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ID and label-verification software enables serialization
Cognex Corporation released its new version of the In-Sight Track & Trace identification-and data-verification solution for healthcare serialization. This version includes enhancements that address additional requirements for pharmaceutical and medical-device manufacturers to achieve unit-level product traceability. In-Sight Track & Trace 2.0 can be used with multiple networked In-Sight vision systems to decode human-readable text along with 2-D and 1-D barcodes, including Data Matrix, GS1-128, GS1 DataBar, securePharm, and Pharmacode. Its pre-programmed add-on software package needs little set up through a touch screen or HMI. In-Sight Track & Trace can be easily integrated into third-party serialization software or MES with industrial protocol support and built-in I/O controls. The technical controls needed for FDA 21 CFR Part 11 validation, including secure user authentication and automatic audit trail generation, are also included.

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Genome editing has played a prominent role in the development of Chinese Hamster Ovary (CHO) cells for biopharmaceutical processes. The DUKXB11 cell line was created in 1980 by introducing mutations in the dihydrofolate reductase (DHFR) locus. Although the engineered cells were not intended for stable recombinant protein production, the DHFR modification provided a potent metabolic selection marker, and the cell line was quickly used to create stably transfected pools.

As knowledge of the CHO genome has increased, many more potential genomic targets have been identified. Genome editing is now routinely used as a tool to aid biopharmaceutical production. When the DUKXB11 cell line was developed in 1980, the only available genomic modification techniques were exposure to chemical mutagens or radiation. Massive screening and selection methods were therefore required to identify cells with the desired genotype. Mutations in the DUKXB11 cell line were introduced by exposing CHO cells to ethyl methanesulfonate or gamma radiation. The cells went through many rounds of selection using [3H] deoxyuridine to isolate clones that contained the desired genotype. These mutagenesis techniques could introduce undesired random mutations throughout the genome and require massive selection strategies to identify clones with the desired genotype. Today, there are several technologies that enable the user to edit the genome more precisely. One of these technologies is the use of zinc finger nucleases (ZFNs).

ZFNs target a specific sequence of DNA and create a double-stranded break (DSB) at that precise location.

Zinc finger nucleases
A zinc finger motif is a natural lyoccurring small protein made up of approximately 30 amino acids, stabilized by at least one zinc ion. Each zinc finger motif binds to a specific set of three nucleotide bases. When several of these zinc finger motifs are connected, they target a precise genomic sequence. A ZFN is formed when a FokI endonuclease is fused to these zinc finger motifs.

ZFNs are designed in pairs that bind to adjacent sequences. When the pair of ZFNs binds to the adjacent sequences, their FokI endonucleases heterodimerize, cutting the DNA at that location. In other words, ZFNs target a specific sequence of DNA and create a double-stranded break (DSB) at that precise location.

Once the DSB has been created, the user can then create specific deletions or insertions at that location, using the natural repair mechanisms of the cell. The precision and accuracy of ZFNs reduce the screening and selection processes needed to identify cells with the desired genotype, reducing timelines.

Other technologies, such as meganucleases or TALENS (i.e., transcription activator-like effector nucleases), can also create targeted changes in a genome. Mega-nucleases (from Precision Biosciences and Cellectis) are restriction enzymes found in single-celled organisms that recognize a large (>20bp) DNA sequence. The disadvantage of this technology is that the protein-engineering process takes several months and cutting efficiencies can be low. TALENS consist of a TALE DNA binding domain that gives sequence-specific recognition, fused to the catalytic domain of an endonuclease. Much like ZFNs, TALENS bind to a specific sequence of DNA and create a DSB. There is, however, a lack of precedence for using them clinically and no clear path to commercial use. In contrast, ZFNs have been used in gene therapy trials. Sigma-Aldrich holds an exclusive license for the ZFN technology through Sangamo Biosciences.

The ZFN technology enables scientists to explore many potential gene modifications that improve cell lines for biopharmaceutical produc-
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tion. The modified cell lines can have characteristics such as improved metabolic selection mechanisms, increased r-protein yield, improved post-translational modifications, and reduced risk profiles.

**Improved metabolic selection mechanisms.** Two widely used selection systems are the DHFR and glutamine synthetase (GS) systems. The ZFN technology can be used to create cell lines with improved selection capabilities by knocking out the endogenous DHFR and GS genes. By improving the selection process, the productivity of the final production clones can be increased.

The DHFR-based selection system requires the elimination of DHFR, an enzyme responsible for purine synthesis. This elimination can be achieved through the addition of methotrexate (MTX), a DHFR inhibitor, or by mutation of the DHFR gene. As previously mentioned, existing DHFR knock-out cell lines were created using mutagens such as ethyl methanesulfonate or gamma radiation. These techniques may have introduced undesired mutations throughout the genome with unknown effects on the cell’s performance. ZFNs allow the user to create a precise knock-out of the DHFR gene without the risk of non-specific mutations.

The GS selection system requires the elimination of the activity of glutamine synthetase, an enzyme responsible for the production of L-glutamine. The activity of GS can be reduced by the addition of methionine sulfoximine (MSX). This approach, however, raises regulatory concerns as well as raw material cost. Targeted ZFN-mediated knock-out of the GS gene eliminates the need for MSX and makes the selection process more stringent.

**Increased r-protein production.** There are several other ways to boost the r-protein yield besides improving the selection process. Genes related to apoptosis can be targeted and knocked out, resulting in longer culture life. Genes that correlate with growth and productivity can be manipulated by changing existing elements that control gene expression.

The ZFN technology enables scientists to explore many potential gene modifications that improve cell lines for biopharmaceutical production.

Another potential method for boosting r-protein yield is a targeted integration approach. Traditionally, r-protein DNA integrates randomly into the genome. Several clones must be screened to isolate a stable, high-producing clone. If a desirable integration region is identified, ZFNs can be used to precisely integrate the transgene at that location, which can lead to higher-producing and consistently stable clones.

**Managing post-translational modifications.** Because of genetic differences between CHO and human cells, r-proteins that are manufactured in CHO cells may have different glycosylation patterns compared with proteins manufactured by human cells. These differences can cause an immunogenic response when the drug is administered to the patient. Two examples of glycosylation differences include Neu5Gc moieties and alpha 1, 3-galactose (alpha-gal) moieties. The genes responsible for these glycosylation patterns are functional in CHO cells, but not in humans. A r-protein produced in CHO cells may therefore contain Neu5Gc or alpha-gal moieties that could cause an immunogenic response when administered. Knocking out the genes responsible for these glyco-proteins can eliminate this risk.

Molecule efficacy can also be increased by engineering glycosylation patterns that increase the residence time of the drug in the bloodstream or by increasing the binding of the Fc region of the antibody to the Fc receptor. The circulating half-life of therapeutic recombinant glycoproteins can be improved by increasing the sialic acid concentration. Targeting genes that increase sialic acid concentrations can increase the residence time of the drug. Increased antibody-dependent cellular cytotoxicity (ADCC) can be achieved by creating antibodies that have greater binding affinity to Fc receptors. Non-fucosylated glyco-proteins have greater binding affinity to Fc receptors, and knocking out genes responsible for fucosylation can result in more efficacious r-antibodies.

Management of post-translational modifications is also important in biosimilar manufacturing, when the glyco-profile of the original product must be matched. In these cases, ZFNs can be used to target genes that impact the glyco-profile to engineer a cell line that can produce a r-protein that matches the innovator material.

**Improved downstream processing.** ZFNs can be used to improve downstream processing by knocking out genes that encode interfering host-cell proteins. If the CHO cell line contains an endogenous protein that copurifies with the r-protein during chromatographic purification, additional and costly steps may be required to remove the endogenous protein. ZFNs can be used to knock out the gene that encodes this endogenous protein. Another potential target may be a protein within the CHO cell that binds the therapeutic r-protein. By knocking out the gene that encodes such a protein, growth and productivity can be improved. The CHO host cell may also produce proteolytic enzymes that could degrade the product before purification. Diminishing protease expression can minimize this effect.

**Risk mitigation.** The risk of prion or viral infection can be mitigated through genome editing. Retroviral titer in a cell could be reduced by targeting and remov-
ing retroviral elements. Additionally, viral uptake pathways can be targeted, conferring resistance to viral attack. Similarly, genes for prion proteins can be targeted and removed.

SAFC has applied the ZFN technology to the development of robust CHO cell lines.

Combining ZFN modifications. Another benefit of ZFNs is that multiple modifications can be performed in the same clone. Desirable ZFN modifications can be trait stacked into the same cell line, enabling the potential development of a “super” CHO line precisely engineered to efficiently produce safe and effective therapeutic proteins.

Genomic changes improve productivity

Genome editing has vastly improved since the creation of the DUKXB11 cell line. Since 2009, SAFC has applied the ZFN technology to the development of robust CHO cell lines by introducing genomic changes that improve the productivity and processing characteristics of biopharmaceutical manufacturing cell lines. More than 30 specific modifications are available to the biopharmaceutical industry. Through microarray experiments, several key genes that impact cell growth and productivity have been identified and explored.

SAFC has several R&D scientists who identify and validate new genetic alterations that are relevant to the biopharmaceutical industry. They have created the CHOZN GS (GS-/-) and CHOZN DHFR (DHFR -/-) knock-out cell lines. Other available cell lines include knock-outs of GGTA (-/-) and CMAH (-/-), which result in cell lines that produce r-proteins without alpha-gal or Neu5Gc moieties, respectively. PT

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Key Take Aways

- Understand what ZFNs are and how they can be used in genome editing.
- Understand the advantages of the ZFN technology in cell-line engineering.
- There are several other ways to boost the r-protein yield besides improving the selection process.
- ZFNs can be used to improve downstream processing by knocking out genes that encode interfering host-cell proteins.
- Genome editing has vastly improved since the creation of the DUKXB11 cell line.
REGULATORY ROUNDUP

More changes at OGD
FDA’s Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) will be headed by agency veteran Kathleen Uhl, pending a broad search for a permanent director. Uhl is stepping in to fill the void left by the surprise departure of OGD head Gary Geba in March after less than a year on the job (see “CDER Runs into Trouble with Generic Drug Reorg Plan” at blog.PharmTech.com). Uhl is not well known in the generic drug industry, but has held a range of important positions at FDA, namely head of the agency’s Office of Women’s Health and most recently deputy director of CDER’s Office of Medical Policy. She faces difficult tasks at OGD—implementing a more efficient application review process, overseeing more-timely field inspections, and establishing the new generic drug user-fee program. A key challenge is to manage a reorganization of OGD to fit plans for CDER’s new Office of Pharmaceutical Quality. Manufacturers have been dismayed by three years of management changes at OGD and hope that Uhl will bring some stability and sense of purpose to the operation. She may hold the job for a while, as it took some two years for Geba to come on board.

FDA budget crunch
Even though FDA fared comparatively well in Congressional action to fund the federal government for the rest of the current fiscal year, which ends Sept. 30, 2013, the agency still has to absorb hefty reductions required by the federal budget sequestration mandate. That mandate imposes a 5% additional cut on current funding, which will compel FDA to tighten up operations and postpone new initiatives. FDA officials have predicted a drop in field inspections and anticipate problems meeting application review time frames, scheduling meetings, developing new guidance documents, and other activities. One important positive development is that the continuing budget resolution approved by Congress just before the end of March authorizes FDA to collect all its user fees, including increases in existing fees and new levies for generic drugs and biosimilars. FDA fee revenues, however, could be subject to the 5% sequester curb; those payments are left in the federal Treasury, further intensifying the squeeze on agency resources.

Supreme Court weighs key drug issues
Two major cases slated to be decided by the high court in June promise to have a major impact on manufacturers and FDA policies, and every legal pundit in Washington is assessing the implications for food and drug law and drug development and marketing. The first case, Mutual Pharmaceutical Co. v. Bartlett (docket no. 12-142), raises questions about whether lower courts can challenge FDA regulatory decisions. A key issue is when and how generic-drug makers should revise labels to reflect important safety issues, even if the changed label differs from that of the innovator product. The case involves a patient who took Mutual’s generic drug and suffered adverse events; the patient sued and won a $21-million judgment based on the company’s failure to warn of the drug’s potential dangers. Mutual argues that the long-marketed, anti-inflammatory drug and its label were approved by FDA, and the Justice Department agrees with the manufacturer and FDA that states can’t override federal regulatory decisions. A ruling in favor of Bartlett would undermine the FDA approval process and open the door to a new wave of drug liability cases. Such a decision also might spur action to revise FDA statute so that injured consumers can sue generic makers, which would gain the right to change labels to add new warnings. This is the third case in recent years that has raised generic-drug safety labeling issues, and there’s growing pressure to clarify the rules.

The second case, FTC v. Activis (formerly Watson Pharmaceuticals) (docket no. 12-416), has received extensive media attention, as it challenges “pay-for-delay” patent settlements between brand and generics manufacturers that determine when a generic competitor comes to market. The Federal Trade Commission (FTC) has long attacked “reverse payment” deals as collusive, anti-competitive, and harmful to consumers and now wants the Court to declare them per se illegal. Brand and generics firms counter that the arrangements avoid costly litigation and actually permit generics to come to market prior to patent expiration. Congressional Democrats have proposed legislation to ban industry settlements and are watching the Court action closely.

FDA articulates benefit-risk approach
As specified by last year’s FDA Safety and Innovation Act (FDASIA), FDA is implementing a standardized approach for assessing the benefits and risks of new drugs and biologics during the application review process. A new five-year plan lays out the agency’s approach (1). Beginning in 2014, FDA reviewers will issue a benefit-risk summary stating the rationale for regulatory action. Approval decisions will consider the severity of the condition treated, available treatment options, and the toxicities of the test product. The agency also will note relevant factors that could raise uncertainties, such as toxicology data, clinical pharmacology, and chemistry, manufacturing and controls information. Although FDA has been incorporating risk-benefit analysis into agency programs and decisions for several years, the plan provides a more “consistent and systematic approach,” which is “exactly what the patient community asked for,” according to the National Health Council. FDA seeks comments on the plan and will update it as necessary.

Reference
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Regulatory Convergence Sought for Global Pharma Market

Manufacturers work with international authorities to harmonize drug registration and supply-chain oversight.

The globalization of biomedical product development is prompting a new look at the barriers erected by divergent national and regional data requirements and policies governing drug production and quality. While efforts to establish common standards for drug testing and product quality through the International Conference on Harmonization (ICH) have streamlined biopharmaceutical development and regulation in industrialized nations, the emergence of more active national regulatory authorities and regional alliances illustrate the need for a broader international approach to setting regulatory requirements. The new goal is convergence of policies and practices, if not total harmonization.

Pharmaceutical manufacturers regard common regulatory policies as key to facilitating access to foreign markets, to patients from other regions for clinical trials, and to lower cost suppliers and operational support, observed Peter Honig, vice-president global regulatory affairs at AstraZeneca. Honig noted the importance of standards in reducing the cost and time of drug development in a February workshop organized by the Institute of Medicine (IOM) Forum on Drug Discovery, Development and Translation (1). In recent years, IOM has examined clinical trial operations and development of medical countermeasures, new treatments for tuberculosis, and drug-diagnostic combinations. This gathering of regulatory authorities and industry leaders from around the world sought to take a fresh look at international regulatory issues in the face of uncertainty about the future of the ICH standards-setting process, concerns about the growing cost of new drug development, and alarm over the increase in substandard medical products in all regions.

In addition to highlighting problems created by divergent clinical research and data requirements, participants emphasized the need for common technical standards to ensure drug quality, reduce redundant manufacturing plant inspections, and help regulators detect substandard products and ensure the integrity of increasingly long supply chains. Individual countries differ in how they implement ICH quality standards, voluntary share redacted GMP information and inspection reports. One encouraging sign is the willingness of more countries to accept inspection standards established by the Pharmaceutical Inspection Convention and Co-operation Scheme (PIC/S) and to voluntarily share redacted GMP information and inspection reports on active ingredients.

Regional networks

Another positive development is efforts by regulatory authorities in Latin America, Asia, and Africa to develop regional standards and cooperative arrangements that reflect local needs and capacities. A clear goal is to attract more pharmaceutical production and investment to spur economic development programs. Regulatory capacity building is a top priority, and benefits from FDA providing technical expertise through the agency’s Forum for International Drug Authorities.

The Pan American Network for Drug Regulatory Harmonization (PANDRH) was established in 2000 by the Pan American Health Organization (PAHO) to promote technical agreements on drug regulation and to build regulatory capacity at national agencies, with the aim of encouraging convergence in drug regulation, explained PAHO senior advisor James Fitzgerald. More experienced regulatory authorities in Argentina, Brazil, Colombia, Cuba, and Mexico have begun to share GMP inspection reports, information on product recalls, and inspection schedules to strengthen oversight activities. A PANDRH GMP working group is developing a harmonized questionnaire for inspections to verify compliance with manufacturing standards based on World Health Organization (WHO) standards; a goal is to provide GMP certificates to firms based on inspections by one of the advanced authorities.

African officials similarly are looking to spur pharmaceutical production in the region to ensure a sustainable supply of quality essential medicines and promote industrial development. The overarching strategy is to shift drug oversight from 54 divergent national regulatory authorities to 5 to 7 regional economic communities with harmonized policies and processes. The over-arching strategy is to shift drug oversight from 54 divergent national regulatory authorities to 5 to 7 regional economic communities with harmonized policies and laws that permit fewer dossiers and clear timelines for drug registration, explained Margaret Ndomondo-Sigonda of the African Union’s New Partnership for Africa’s Development. Under the Medicines Registration Harmonization Project of the East African Community (EAC), for example, health and regulatory officials are developing guidelines on label formats, patient information leaflets, stability requirements, and registration forms. A GMP technical working group is finalizing a GMP inspection manual, standard operating procedures for conducting GMP inspections, and formats for writing GMP summaries and reports.

Mike Ward, manager of international programs at Health Canada, outlined efforts by the Asia-Pacific Economic Cooperation (APEC)

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Vaccine development
Vaccine development and oversight provides a prime area to test harmonization approaches. The African Vaccine Regulatory Forum (AVAREF) brings together regulators and ethics committees to examine and jointly review applications from vaccine manufacturers seeking to conduct clinical trials in the region. Such a process not only promotes convergence, but also can build “mutual trust” between neighboring countries as participants can see the quality of inputs from their peers, noted David Wood, WHO coordinator of quality, safety, and standards for vaccines and biologicals.

One danger is that collective efforts to establish common regulatory approaches among national authorities will lead to policies and standards that differ between key regions. To achieve simultaneous global drug development and near-simultaneous registration around the world, said Honig, all parties have to agree on expectations for clinical-trial operations, pharmacovigilance processes, and data transparency. The role of regulators, said Douglas Throckmorton, deputy director, Center for Drug Evaluation and Research, is to provide clarity on rules and regulations and to ensure a level playing field between domestic and foreign manufacturers. Harmonization requires regulators to “give up some control” over their policies and programs, observed Deborah Autor, FDA deputy commissioner for global regulatory operations and policy. She urged workshop participants to further articulate the business case for global regulatory convergence, spelling out the gains and efficiencies it can provide, and a plan for addressing key gaps to get global coalitions moving. Steven Galson, vice-president for global regulatory affairs at Amgen and co-chair of the workshop, said the next step is for industry and regulators to craft an economic analysis documenting the enormous savings in resources from harmonization. The parties represented at the gathering, he commented, have the power, force, and creativity to “go forth and converge” and should do so without delay.

Reference
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Should Regulation of Combination Products Become More Centralized in Europe?

While there are those who want combination products to be controlled by a centralized pharmaceutical-type approval system, the majority of the medical technology industry wants to retain a decentralized device-focused approach.

Combination products in the European Union (EU) are currently regulated through two different arrangements. Combinations comprised solely or mainly of pharmaceutical actives are controlled by medicines agencies while those consisting predominantly of devices are approved through a fragmented national-based system based on certification by an expert organization called the Notified Bodies. However, European politicians, non-governmental organizations (NGOs), doctors, and sections of the pharmaceutical sector have been calling for the regulation of combination products to become more centralized. This approach would make it more similar to the system in the United States where FDA approves combination products whether they are pharmaceuticals or devices.

EMA’s role
The pressure for a more centralized approach has intensified after the European Commission proposed revisions to the existing EU legislation on medical devices, with the aim of putting more emphasis on patient safety. The Commission suggested that the European Medicines Agency (EMA) take a wider and more active responsibility for the scientific assessment of some in vitro diagnostic devices such as the companion diagnostic tests (CDTs). European Biopharmaceutical Enterprises (EBA) has cautiously welcomed the Commission’s proposal that EMA should participate in the assessment of clinical evidence on the scientific validity of companion diagnostics.

“The proposed involvement of EMA in the assessment of companion diagnostics could prove beneficial, provided that the regulatory obligations and research efforts to provide clinical evidence are not duplicated,” says Titta Rosvall-Puplett, executive director of EBE.

Device regulation
Members of the European Parliament and some NGOs want the Commission to be much tougher with devices outside the diagnostics category by proposing the introduction of premarketing authorization (PMA) of high-risk or Class III products. This relatively large group of medical devices would then have to undertake an approval procedure similar to that applied to pharmaceuticals. Some EU member states, such as France, have hinted that they might support the idea of PMA for these devices. Inevitably, EMA is seen by PMA supporters as the appropriate body to carry out premarketing approval based on data from pharmaceutical-style preclinical and clinical trials.

“A premarketing authorization system for high-risk devices, such as that run by FDA in the US, is needed in Europe because the safety challenges for these products is similar to those for medicines, and in some cases, the hazards could be even more severe,” says Monique Goyens, director general of the European Consumer Organization (BEUC). “You can stop taking a medicine if something goes wrong, but with a deficient medical device, the patient may require surgery,” she continues. “EMA has the right infrastructure and experience to do the premarketing assessment work.”

The medical devices sector, led by its main trade association Eucomed, has recognized that the legislation needs to be overhauled after a number of scandals. The biggest of these scandals came to light three years ago after a leading French devices manufacturer, Poly Implant Prothese (PIP), used industrial rather than medical grade silicone for making breast implants. The industry supports the Commission’s proposed introduction of higher safety and quality standards among the Notified Bodies. It also backs more stringent requirements for clinical evidence to demonstrate the efficacy of higher-grade devices.

However, the medical devices sector is unhappy about the Commission’s move to set up a central body of member state representatives—the Medical Device Co-ordinating Group (MDCG)—to conduct an additional “scrutiny” procedure on risky devices. It is even more concerned about any initiative to bring in PMA, especially if it is operated by EMA.

“What we want is a device-specific, effective, and predictable approval system that guarantees the highest safety for patients without necessary delays, (and which is) specifically important for the highest risk class of devices,” Serge Bernasconi, Eucomed’s chief executive, told a European Parliament workshop on the revised legislation in February 2013. He claimed that a centralized approval system would not work for patients and the industry. He cited research conducted last year by the Boston Consulting Group (BCG) showing that devices have been approved and made available to patients in Europe at least three years before the same devices were approved in the US.

Class III products
The high-risk Class III products incorporate substances that would be classified as medical products if marketed separately but in a combination, they enhance the functioning of the device itself. This group includes intra-uterine contraceptives and devices such as the heparin-coated catheters and bone-cement containing an antibiotic. With improvements in combination technologies, the distinction between what is primarily a device...
or a medicine has become harder to determine. In Europe, there has been a growing number of Class III combination products in recent years, whereby the drug and device are so closely integrated that one cannot be considered to be clearly ancillary or supplementary to the other. Furthermore, the materials and active ingredients can affect the function of each other.

“Under the present system, this interaction between the drug ingredients and the device materials is not being properly analyzed or assessed,” says Goyens. “It needs to be done by an independent body with a public health mission and not by the Notified Bodies without any public health mission.”

Although EMA has not been openly touting the EU for a key role in the assessment of devices, the agency’s executive director, Guido Rasi, spoke out in an interview with Reuters last year in favor of regulating devices “at the same level of science and attention as with drugs.” The agency clearly wants to establish a strong position in the assessment of combination products in areas of innovative medicine, such as advanced therapies and nanomedicines in which drugs and devices are closely integrated.

EMA’s committee for advanced therapies (CAT) already has an advisory group that acts as the Notified Body for certifying devices for gene and cell therapies, and tissue engineering. Last year, the agency started issuing public assessment reports (PARs) on pharmaceutical substances combined with biological devices. The reports included details of the safety and quality of the pharmaceutical while looking at the benefits of its integration with the biologics devices such as scaffolding.

Nonetheless, some observers doubt whether EMA has sufficient competence to assess both pharmaceuticals and devices, and the interactions between the two. “In my experience, people from pharmaceutical backgrounds can struggle with medical devices because of different approaches to the interpretation of the data,” says Peter Rose, managing director of High Edge Consulting, Nottingham, England. “The device experts are much better at stepping up to the role of medicines assessment whereas with the pharmaceuticals specialist, it is the reverse.”

There may have to be a compromise by incorporating elements of both centralization and decentralization without having to bring together expertise in pharmaceuticals and devices within one organization. “Evaluators of the drug and the device need to work more closely together with a sharing of evaluation data at some stage, but the evaluators do not necessarily need to be working in the same entity,” says Marielle Fournier, director of Voisin Life Sciences Consulting, London.

Ultimately, the key decisions on the revised or recast legislation on medical devices will be taken by the European Parliament and the Council of Ministers of governments of EU member states. As the changes are unlikely to be approved until next year at the earliest, there is plenty of time for the centralizers and decentralizers to resolve their differences.
André Schmidt
Graduated engineer (Technical University)
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Brazil's regulatory chamber of pharmaceutical products market (Anvisa-CMED) has authorized pharmaceutical products in the country to have prices adjusted by up to 6.31% starting on March 31, 2013, according to Anvisa, an agency that monitors drug prices and gives technical support for the definition of drug prices. One of the agency's attributions is the Executive Secretariat of the Drug Market Regulation Chamber (CMED), which is an interministerial body responsible for drug market regulation and for establishing criteria of drug prices definition and their adjustments.

Anvisa, led by the Ministry of Health, has set percentages for raising the price of antibiotics, anti-inflammatory agents, diuretics, and other drugs. Homeopathic and naturopathic products are not subject to such price increase. The cap-price determined will be frozen either for a one-year period or until March 2014. According to the Brazilian Pharmaceutical Wholesalers Association (Abafarma), the percentages vary between 2.70%, 4.59%, and 6.31%, and were stipulated based on the market share of each product in the local market in comparison with generic brands of the same drug. As Abafarma executives note, the only products in Brazil to have price controls are pharmaceutical drugs.

**Price-cap regulation**

Since 2003, Anvisa's regulatory chamber has managed price controls of pharmaceutical drugs commercialized in Brazil by setting price-cap standards. The "production" price-cap defines the maximum wholesale price at which a pharmaceutical drug may be sold in the Brazilian market, while the "consumer" price-cap is the maximum price at which it can be sold to the customer at drugstores and pharmacies around the country.

The regulatory authority defines the maximum price of pharmaceutical drugs through CMED's Resolution 2/2004. New drugs entering the market will be put in categories and priced according to their use and scientific evidence according to the regulatory authority. When considering the price-cap for new pharmaceutical products, the local authority will also evaluate the lowest international price for that product using certain countries as a parameter, including the country where the drug was produced, as well others such as the United States, Canada, Spain, Italy, Portugal, Greece, France, Australia, and New Zealand.

**Control benefits**

The study, released in January 2013 by Anvisa, analyzed pricing standards in the past years and concluded that the current pricing regulation has enabled Brazilians to purchase pharmaceutical drugs at prices that are on average 35% lower than the values initially requested by the pharmaceutical industry. The study evaluated the prices of pharmaceutical products containing new molecules, drugs to be sold in new pharmaceutical forms, and new associations for known active ingredients. The study showed that new associations of active ingredients enter the market at lower prices than the ones presented to Anvisa by pharmaceutical companies because of the established price-cap market regulation, which impeded companies from charging higher values. The study evaluated the prices of pharmaceutical products containing new molecules, drugs to be sold in new pharmaceutical forms, and new associations for known active ingredients. The study showed that new associations of active ingredients enter the market at lower prices than the ones presented to Anvisa by pharmaceutical companies because of the established price-cap market regulation, which impeded companies from charging higher values.

The study analyzed cap-prices established by CMED between March 2004 and December 2011 for 1115 formulae/presentations and 433 pharmaceutical drugs.

According to the management of Anvisa, the prices of pharmaceutical drugs entering the Brazilian market ended up lower than those presented to Anvisa by pharmaceutical companies because of the established price-cap market regulation, which impeded companies from charging higher values. The study evaluated the prices of pharmaceutical products containing new molecules, drugs to be sold in new pharmaceutical forms, and new associations for known active ingredients. The study showed that new associations of active ingredients enter the market at lower prices than the ones presented to Anvisa by pharmaceutical companies because of the established price-cap market regulation, which impeded companies from charging higher values.

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Lyophilization, or freeze drying, is an important manufacturing step widely used to increase the stability of pharmaceutical and biological products. Developed during the 1940s, lyophilization produces a dry product that can be readily reconstituted to its original form by adding water when required (1). It prolongs product shelf life by inhibiting chemical, microbiological, and physical degradation pathways that occur in the presence of moisture, particularly where long periods of storage and transit prior to use are involved (1, 2).

The lyophilization process consists of three main stages—freezing (solidification), primary drying (ice sublimation), and secondary drying (moisture desorption)—and usually takes several days to complete. Multiple vials containing a liquid drug formulation are loaded on temperature-controlled shelves within a sterile chamber and cooled to low temperatures until completely solidified (2). After that, chamber pressure is reduced and shelf temperature is raised to remove the frozen solvent through sublimation. The remaining unfrozen solvent that is chemically bound to the solid product is removed by a desorption process (3). The drying process is concluded by stoppering the vials in the chamber, generally under a subambient pressure of inert gas. The final dry product, called a cake, usually occupies approximately the same volume as the initial liquid fill because of its high porosity (2).

“To ensure that high quality products are consistently produced, it is crucial to be able to control and provide repeatability of the lyophilization cycles,” says Joseph Brower, technology manager at IMA Life North America.

The freezing step

During the freezing phase of a typical freeze-drying cycle, the nucleation process of which the first solid domains are formed occurs randomly in the vials. “In an uncontrolled environment, due to the lack of nucleation sites in pure systems, the formulation solution must be cooled down to temperatures that are significantly lower than the equilibrium freezing point (i.e., supercooled) to initialize formation of ice crystals,” Brower explains.

The contents of individual vials often nucleate or begin freezing over a broad range of temperatures, “usually spanning 10–15 °C below the formulation’s thermodynamic freezing point in a laboratory freeze dryer and 20 °C or greater in a cGMP Class 100 production dryer,” says Mark Shon, vice-president of sales and marketing at SP Scientific. This supercooling phenomenon creates significant vial-to-vial heterogeneity in the solid microstructure, which significantly affects the subsequent drying processes. “To accommodate this heterogeneity, today’s best practice is to design lyophilization processes for the worst-case scenarios; however, this strategy can result in excessively long drying cycles, broad product specifications, longer process development times, and nonoptimal product preservation,” comments Cheryl...
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It has long been recognized that one of the most important goals during the freezing step of lyophilization is to produce a uniform batch, which is a challenge due to the stochastic nature of nucleation. The random nature of nucleation, however, makes it difficult to control the nucleation temperature and maintain it within the desirable supercooling range.

Implications of uncontrolled nucleation

The nucleation behavior can affect several lyophilization process steps and product attributes. “The implications of uncontrolled nucleation are several-fold,” says Shon.

One of the most important goals during the freezing step of lyophilization is to produce a uniform batch.

“First, since every vial can nucleate at a slightly different time and temperature, true vial-to-vial uniformity is really not achievable. We have seen a vial nucleate at -7 °C and another vial (of the same type with the same product) nucleate an hour later at -18 °C. These vials are now very different. They will dry at different rates and have a different pore structure, different cake structure, and different specific surface area.”

Nucleation of freezing strongly influences the size of the resulting ice crystals. Studies have demonstrated that colder nucleation (i.e., higher degree of supercooling) generally produces smaller and more numerous ice crystals, which leave behind smaller pores upon sublimation in primary drying. “These smaller pores present a greater resistance to subsequent sublimation of the remaining ice. As a result, primary drying is slowed by cold nucleation temperatures,” explains Thierfelder. “The longer cycles stemming from uncontrolled nucleation require increased investment in lyophilization capacity and higher operating costs. It also means greater risk as the product sits in a vulnerable multiday batch operation.”

On the other hand, a lower degree of supercooling produces larger ice crystals that result in large pores during drying, reduced resistance to mass flow, and shorter drying times. “Studies have shown that primary drying times were extended 1–3% for every 1 °C change in ice-nucleation temperature (5, 6). Therefore, by reducing the degree of supercooling from, for example, 15°C to 5°C for uncontrolled and controlled nucleation respectively, the primary drying time can potentially be decreased by 10–30%, which is significant given the fact that primary drying may take days,” says Brower.

“Reduction in primary drying time is one of the significant benefits of controlled nucleation,” Shon adds. “A number of research groups have reported as much as a 40% reduction in primary drying times (7–9). This can have a significant financial impact on production as throughput can be significantly increased without increasing the number of expensive production dryers.”

Besides influencing the size of ice crystals, the nucleation behavior can also affect product yield in various ways. For example, previous research has shown that proteins tend to aggregate on the surface of ice (10–14). Colder nucleation tends to produce smaller ice crystals, which possess larger surface areas; therefore, colder nucleation creates increased aggregation stress on sensitive proteins.

Another potential source of yield loss in lyophilization arises from vial cracking. “The exact mechanisms for vial cracking are not well understood, but the problem seems to occur when certain formulation components are improperly frozen into metastable states that rearrange upon heating in primary drying, and sometimes this rearrangement creates sufficient force to crack the glass container,” Thierfelder explains. “The temperature at which nucleation occurs affects the kinetics of the freezing process and can influence vial-cracking phenomena.”

Uncontrolled nucleation can adversely affect product quality. “No matter how well engineered your process controls or how uniform your freeze-dryer’s heat-transfer environment might be, vial-to-vial uniformity is impossible to achieve in the absence of controlled nucleation,” Thierfelder notes. “The vials will nucleate at random temperatures and times, and therefore, have separate temperature histories, which will impart different properties to the freeze-dried product.”

Nucleation and freezing also affect the cosmetic properties of cakes with effects such as glazing, cake cracking, and stratification often resulting from problems during the freezing step. “Overall, it should be recognized that the traditional lack of control over nucleation behavior is poorly aligned with FDA’s current emphasis on quality by design,” Thierfelder adds.

Controlled nucleation

A successful lyophilization cycle is defined by dried products that are visually and functionally acceptable, and chemically and biologically stable, with a short reconstitution time. “Although ice nucleation is an important parameter for achieving homogeneous product and optimized cycles, there have been very few attempts to achieve it at a commercial scale until recently,” observes Brower. The standard practice has been to use an annealing cycle, which involves raising the product temperature after freezing to a temperature above glass transition, and then holding it. This method results in the formation of larger ice crystals at the expense of smaller ones, and helps minimize the variability in drying behavior (15). Brower, however, points out that the benefits of shorter drying times may be offset by the additional time required for the annealing cycle. Moreover, annealing fails to address the root cause of variable ice structure, which is the lack of a uniform ice-nucleation temperature, and can only help to mitigate a flawed condition (15).

Controlled ice nucleation involves cooling the entire batch of vials to a given selected temperature that is below the equilibrium freezing point but above the temperature at which spontaneous heterogeneous nucleation may occur (16). Nucleation is then induced by seeding the vials with ice crystals or by depressurizing the freeze-dryer chamber.
For successful controlled nucleation, each vial of product must experience the same conditions at the same time.

developed by Praxair). “The method of controlled nucleation, whether by injecting ice crystals or depressurization, has no material difference on the initial ice structure,” says Thompson. “The key to successful crystal formation is a common starting point and the control of crystal growth after the nucleation event.”

In the ice-fog technique, the vials are first cooled to the desired temperature below the equilibrium freezing point and the pressure is reduced to approximately 50 Torr. Cold nitrogen gas is then introduced (through a liquid nitrogen heat exchanger) into the chamber. The cold gas in the humid chamber forms an ice fog, which is forced into the vials to seed ice crystallization in the supercooled solution (16). In short, ice fog generates “seed” crystals that fall into the vials creating the “nucleus” around which ice crystals form during nucleation.

On the other hand, the depressurization technique involves reducing the product temperature in all vials to a selected value, followed by pressurization of the freeze-dryer chamber with an inert gas such as nitrogen or argon. When thermal equilibrium has been achieved, the excess pressure is released rapidly (i.e., depressurization), causing ice crystals to form at the top of the solution and propagate throughout the vial within seconds (16). With this method, ice formation is induced at essentially the same time for all vials in the batch, in contrast to the ice-fog technique where the vials are nucleated within a minute or two.

Thompson, however, points out that a consistent crystal structure in the vial and across the batch is not produced by merely controlling the shelf temperature at a specific ramp rate. “Controlled nucleation provides a method to create a consistent starting point for crystal formation, but by itself only provides moderate improvement of crystal structure. Controlled nucleation needs to be combined with controlled crystal formation to produce the most homogeneous and efficient crystal structure inside the vial and throughout the batch,” Thompson explains. Once controlled nucleation has occurred, a method for measuring and controlling the crystal growth is needed.

Ice-fog technologies
Millrock’s patented FreezeBooster controlled nucleation technology combined with the company’s patent pending AccuFlux technology is an ice-fog approach that allows the crystal structure to be consistently created, monitored, and controlled. According to Thompson, the combined methods of FreezeBooster and AccuFlux produce a consistent and repeatable ice formation resulting in a highly uniform finished product with reduced primary drying times.

“To reduce drying times and produce a consistent product, control of the entire freezing process is required,” explains Thompson. “Millrock’s AccuFlux technology enables crystal growth to be monitored and controlled even though the temperature of the product is not changing. It provides the tool necessary to accurately and repeatedly transfer protocols from the laboratory to production. It also provides a tool for simulating production protocols in the laboratory, which is useful for determining production problems.”

The Veriseq nucleation technology, developed by Linde Gases in cooperation with IMA Life North America, offers a commercially viable technique for cryogenically generating a uniform dispersion of microscopic ice crystals as a result of contact between liquid nitrogen (produced from sterile-filtered gaseous nitrogen) and steam in a mixing device outside the lyophilization chamber. Upon introduction into precooled vials containing the product to be freeze dried, these ice-fog crystals serve as nucleation sites, which cause rapid and uniform nucleation of the product in a vial as well as between vials of the same batch at very low degrees of supercooling.

“A key challenge for the commercial implementation of Veriseq nucleation technology was to generate sufficient amount of ice-fog and ensure its penetration inside the vials given various lyophilizer volumes,” observes Brower. “Efficient ice-fog generation and distribution were achieved using the ejector assembly, providing an extremely efficient way of quickly forming the ice fog and circulating it throughout the freeze chamber.”

A recent case study involved the use of Veriseq nucleation technology on a product that required a long (120-hour) lyophilization cycle (17). Conservative cycle parameters had to be employed because of the thickness and concentration of the frozen material. Attempts to reduce cycle time by adding more heat to the process resulted in broken containers. By using Veriseq nucleation technology to increase the crystal size, it was possible to accelerate drying with no breakage and reduce cycle time to 80 hours (17).

Depressurization technique
For successful controlled nucleation, each vial of product must experience the same conditions at the same time. “ControlLoyo technology is based on pressure and each vial, regardless of shelf location or tray position, experiences exactly the same conditions at exactly the same time,” says Thierfelder. “For this reason, ControlLoyo technology is successfully used from laboratory to manufacturing scale.”

ControlLoyo Nucleation On-Demand technology was developed by Praxair
And licensed to SP Scientific exclusively for use on dryers with shelf areas of less than 1.0 m² and nonexclusively on larger dryers. This technology allows users to select the temperature at which they want to nucleate. The selected temperature must be below the true freezing point of the product and above the temperature at which stochastic nucleation tends to occur on the surface of ice crystals and is synonymous with yield loss and potential adverse effects. ControLy technology to a production dryer, “It does not require that the dryer be manufactured with the capability to perform the controlled nucleation.” Shon explains that it is relatively easy to retrofit a commercial freeze dryer that has steam-in-place (SIP) capability with the manifolds and controls to do the pressurization/depressurization required for Controlled technology. “In the largest scale-up study to date, we collaborated with Fresenius-Kabi and performed a retrofit on a 28-m² production dryer (19). The dryer was fully loaded with 100 mL, 50 mL, 30 mL, and 20 mL vials with 5% mannitol solution. Nucleation was controlled and every vial was visually inspected to confirm complete nucleation. In total, 8701 vials were nucleated (19).”

To reduce drying times and produce a consistent product, control of the entire freezing process is required.

Lyophilization

and licensed to SP Scientific exclusively for use on dryers with shelf areas of less than 1.0 m² and nonexclusively on larger dryers. This technology allows users to select the temperature at which they want to nucleate. The selected temperature must be below the true freezing point of the product and above the temperature at which stochastic nucleation tends to occur on the surface of ice crystals and is synonymous with yield loss and potential adverse effects. ControLy users have reported a reduction in protein aggregation (14).

- Reduced vial cracking: Some lyophilized products have an amorphous structure and some have a crystalline structure. Others, such as those formulated with mannitol, can freeze in either an amorphous or crystalline structure. Upon initial freezing, certain products with the ability to form amorphous or crystalline structures will orient in an amorphous structure. During an annealing cycle (i.e., freeze, warm, and refreeze), the product is forced into its crystalline structure. In the absence of annealing, some products may randomly transition during processing, resulting in vial cracking. Vial cracking is costly and disruptive. In general, it has been observed that cracking problems can be substantially mitigated using ControLy technology to induce nucleation at warmer temperatures (18). A number of studies have been conducted where we have scaled-up ControLy technology to a production dryer,” says Shon. “It does not require that the dryer be manufactured with the capability to perform the controlled nucleation.” Shon explains that it is relatively easy to retrofit a commercial freeze dryer that has steam-in-place (SIP) capability with the manifolds and controls to do the pressurization/depressurization required for ControLy technology. “In the largest scale-up study to date, we collaborated with Fresenius-Kabi and performed a retrofit on a 28-m² production dryer (19). The dryer was fully loaded with 100 mL, 50 mL, 30 mL, and 20 mL vials with 5% mannitol solution. Nucleation was controlled and every vial was visually inspected to confirm complete nucleation. In total, 8701 vials were nucleated (19).”

References

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Optimized freeze-drying cycles can offer scientific and business advantages.

Freeze drying, or lyophilization, is a stabilization method that is widely used in the pharmaceutical industry for drugs, vaccines, antibodies, and other biological material. Because the product is dried without excessive heating, proteins and other products that would be thermally denatured can be successfully preserved without loss of activity.

Freeze-dried products have a very high surface area, which enables them to be reconstituted quickly. This quick reconstitution is particularly important in the case of emergency vaccines and antibodies, which need to be administered as soon as possible.

Every formulation has different freeze-drying characteristics and, therefore, different processing requirements. To ensure cycles are both robust and efficient, they should be tailor-made for each formulation. Failure to do so can lead to inconsistent dryness across samples, reduced stability during storage, and reduced activity on rehydration.

There are three main business advantages of optimizing a product’s lyophilization cycle:

- **Financial gain:** optimal lyophilization cycles use only the energy and time required, shortening process time and increasing product throughput.
- **Product excellence:** a well-dried product exhibits a long shelf life and maximum activity on rehydration.
- **Quality and regulatory assurance:** consistency throughout batches is assured and regulatory submissions are completed with the inclusion of lyophilization cycle data.

The freeze-drying cycle

Lyophilization is a complex drying process that involves removing the solvent from a material by sublimation. Sublimation is achieved through varying the temperature and pressure of the material so that the solvent does not pass through the liquid stage, but moves directly from the solid phase to the gas phase (see Figure 1). Lyophilization takes place in three main stages: freezing, primary drying, and secondary drying. Each stage has its own challenges.

**Freezing.** The material is frozen. The rate of freezing, and the final temperature to which the material is lowered, both have a significant impact on the quality of the final product. The rate at which the temperature is lowered affects the structure of the ice matrix, which has an impact on the ease of flow of the sublimated vapor out of the sample. Annealing, a technique of raising and then lowering the temperature of a frozen material, can be used to encourage crystallization or to provoke a more favorable ice structure.
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In delicate materials such as proteins, there is a risk of damage from ice crystal growth. In general, the faster the rate of freezing, the larger the ice crystals formed and the greater the risk of damage. A slower freezing cycle will result in smaller crystals that cause less damage, but the resulting structure will cause a greater impediment to the flow of vapor and therefore slow the drying process.

During the freezing stage, it is vital that the material is cooled below its critical temperature (T_{crit}) to ensure it is fully frozen. Every formulation has a different T_{crit} that is affected by the combination and proportions of the elements within it, such as the solvent, excipients, and the active ingredient. It is vital that the critical temperature is determined for every different formulation. Knowing the T_{crit} not only makes it easy to ensure that the T_{crit} is achieved during freezing, but also means that energy is not wasted by taking the temperature lower than required. Methods for determining T_{crit} are discussed below.

**Primary drying.** The frozen material is initially dried by sublimation. During primary drying the pressure of the drying chamber is reduced to a very low level, while the temperature is raised slightly to allow the solvents to sublime. Throughout this stage the temperature must be kept below the critical temperature (T_{crit}) so that the material does not melt or its structure collapse.

One of the effects of sublimation is cooling of the product, which slows the process of drying. The rate of sublimation can decrease by as much as 13% for each unnecessary 1°C decrease in temperature (1). To counter this cooling and provide energy to drive the sublimation process, heat is added through the freeze-dryer shelf. The energy transfer during primary drying must be balanced so that sufficient heat is used to encourage sublimation without risking collapse.

Collapse is the most serious processing defect in freeze drying, resulting in reduced shelf life, reduced stability, decreased product activity, and poor reconstitution (see Figure 2).

**Secondary drying.** Secondary drying is a desorption process that removes any solvent that is left chemically bound in the material after primary drying. The moisture level at the beginning of this stage may be around 5–10%, with a final moisture content of typically less than 5%.

To facilitate the desorption process, the temperature is raised and the pressure reduced to a minimum (see Figure 3). This is the slowest phase of the lyophilization process. Depending on the final moisture level required, it could last several days. Therefore, any increases in efficiency can have a significant impact on manufacturing throughput.

**PRODUCT CHARACTERIZATION FOR CYCLE DEVELOPMENT**

Fully characterizing each formulation provides the data necessary to ensure that the cycle designed is optimal for the product and the equipment. Without this information, there is no way to determine the basic process parameters or to scientifically verify the success of the resulting cycle.

Process conditions that are too aggressive will damage the product, decreasing stability and activity, and risking complete batch failure. Process conditions that are too conservative will add unnecessary energy costs, increase batch duration, and reduce turnaround time. A poorly designed cycle can experience some or all of these problems.

**Collapse temperature.** The most important characteristic of a material for freeze drying is its critical temperature. In simple crystalline materials this is the eutectic temperature (T_{euc}), although more commonly the collapse temperature (T_c) is relevant. T_c is applicable to products which will form amorphous solids, such as pharmaceutical formulations.

T_c and T_{euc} are typically ascertained using freeze-drying microscopy (FDM), a quick and well-understood process in which a small amount of product is frozen under a microscope. FDM can be carried out on quantities as small as 70 µL (2). Such quick feedback makes it feasible to check the freeze-drying...
characteristics of each new product formulation, helping the formulation technologist understand the product’s response to freeze drying. In the interests of achieving optimum efficiency, FDM can also be used to determine the relative rates of drying for different formulations, or for the same formulation at different temperatures.

In addition to the identification of critical temperature, FDM can also provide a visual indication of the potential for skin formation and the effects of annealing on the ice structure, solute crystallization, and critical temperature.

**Frozen state mobility.** It is common to think of freezing as a simple, discrete process whereby something is either a solid or a liquid. However, in complex formulations comprising many separate elements, solidification cannot be relied on as an indication of complete freezing and changes may still be taking place within the frozen structure.

A solid that has a non-crystalline (amorphous) structure is referred to as a glass and the point at which the product changes from a liquid to solid is known as the glass transition temperature (Tg). However, due to the complex nature of most pharmaceutical and biotechnological products, glass transition occurs over a range of temperatures. Changes in molecular mobility can occur even in product frozen below its collapse temperature, and these changes can have significant impact on the product’s shelf life and long-term activity.

In the event that changes are taking place in the frozen state, it may be necessary to adjust the cycle or to adjust the formulation. However, in most cases the possibility of frozen state flexibility is ignored until problems with the dry product occur. To avoid late-stage redevelopment work, it is advisable to conduct the analysis early on in cycle development, ideally at the same time as FDM.

Typical frozen state analyses include differential scanning calorimetry (DSC) and joint differential thermal analysis (DTA)/impedance analysis.

DSC is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. DSC is used to detect physical transformations such as phase transitions, endo- or exo-thermic events such as crystallization events, and glass transitions.

DTA is a technique similar to DSC. When used in conjunction with impedance analysis (ZSinΦ), a fixed frequency dielectric analysis, the molecular mobility of a frozen sample can be explored to a very high degree of accuracy.

**Refining the cycle**

Once initial cycle parameters have been defined, the next step is to run a test batch on a research freeze dryer with product monitoring capabilities. Monitoring process conditions such as chamber pressure and product temperature enable the endpoints of primary drying and secondary drying to be determined.
The emerging field of peptide and protein therapeutics is responsible for a new therapeutic era. Peptides are attractive therapeutic molecules due to their high specificity and potency. Peptides biodegrade into nontoxic or low toxicity metabolites, with minimal potential for drug–drug interactions and low immunogenicity compared to larger proteins. These advantages are reflected in a regulatory approval rate of more than 20% probability, which is double that of small molecules (1). The average number of new candidates entering clinical evaluation every year has steadily increased from 1.2 per year in the 1970s to 4.6 per year in the 1980s, 9.7 per year in the 1990s, and 16.8 per year in the 2000s (2).

Peptides were not favored as drug candidates because of their physicochemical characteristics and the necessity for expensive and complicated manufacturing processes. Peptides often have short half-lives (of less than 20 minutes), thereby making chronic administration problematic and costly. Two major technological advances contributed to the industrial acceptability of peptide-drug candidates:

• Advances in genetic engineering, recombinant technologies, and solid-phase peptide synthesis overcoming the problems of high cost of manufacture as well as stability issues of peptide molecules
• Advancements of polymer technologies allowing controlled long-acting release formulations of peptides encapsulated in biodegradable polymers such as the gonadotrophin-releasing hormone (e.g., goserelin acetate [Zoladex, AstraZeneca]).

Today, the most important drawback in translating peptides into clinically useful therapies is the lack of adequate oral bioavailability. As the preferred route of administration for medicines is the oral route, and given the lack of patient compliance with therapeutics that require chronic self-intravenous administration, the pharmaceutical industry originally opted to focus its efforts on the development of oral alternatives for peptide-based drugs.

Due to the increasing cost of R&D and the decreasing number of approved drugs, new alternative approaches are needed to boost the productivity of the pharmaceutical industry (3). Parenteral administration of peptides is usually painful, and requires sterile manufacturing or aseptic processing of thermally unstable biomacromolecules. Technologies that enable the delivery of biologicals across mucosal barriers, such as the gastrointestinal tract (GIT), the nasal mucosa, and the blood-brain barrier (BBB), therefore, offer potential for the development of effective and safe noninvasive biologicals, and can enhance the commercial success of peptide therapeutics.
Controlled-release technologies

The major challenge in peptide delivery stems from their low physicochemical and proteolytic stability as well as poor permeation across biological barriers in the absence of a specific transport system, which is due to their hydrophilicity, charge, and high molecular weight (> 500 Da). Peptides routinely violate the majority or all of Lipinski’s predictors for good absorption and bioavailability (4).

Traditional drug development of peptides and proteins has relied on parenteral injection of liquid formulations as the fastest and often least expensive route to commercialization.

Following parenteral administration, the peptide drug is subjected to extensive degradation in the bloodstream, often resulting in a short plasma half-life. In addition, the peptide drug is also subjected to metabolism by liver enzymes and clearance by the kidneys (5). Linear peptides possess high conformation flexibility that can result in peptide denaturation and poor targeting to the tissue of interest, which can further result in poor shelf stability.

Traditional drug development of peptides and proteins has relied on parenteral injection of liquid formulations as the fastest and often least expensive route to commercialization. The key drivers for selecting a peptide delivery method for commercial development include patient convenience and compliance, requirement for local or topical delivery, systemic toxicity or other safety issues, as well as market competition. The latter driving force, combined with research efforts, has led to the development of controlled-release technologies for peptide delivery by parenteral routes (e.g., intramuscular or subcutaneous) and prompted the development of technologies for noninvasive peptide delivery. The oral, nasal, and pulmonary approaches are the focus of the pharmaceutical industry while transdermal and ocular technologies are researched because these routes are preferred for achieving local levels able to elicit therapeutic benefit.

Factors that determine the selection and development of an appropriate delivery system and route of administration are the therapeutic dose and release profile required, the duration of treatment, the disease conditions, and target patient population (intravenous injections or infusions for hospitalized patients, and higher patient compliance systems for out-patients). Additional factors include the impact of processing conditions on stability and bioactivity of peptides and proteins to avoid increase in immunogenicity or loss of efficacy, and finally, the bioavailability by means of the particular route and delivery system chosen (6).

Implants, capable of releasing peptides in a controlled manner for a desired length of time, are clinically important systems for prolonged release of proteolytic labile peptides. However, zero-order release kinetics usually achieved with these systems (i.e., ability to deliver a drug at a rate that is independent of time with the concentration of drug within a pharmaceutical dosage form) are not always the best delivery regimes compared with pulsatile systems because down-regulation of receptors can occur.

As an alternative to repeated injections or infusion pumps, depot-delivery systems provide continuous peptide delivery after a single administration, usually with a frequency of once-monthly or three-monthly for chronic conditions. Depot-delivery systems can be divided into four major groups: implants, microspheres, nano-particles, and injectable solutions such as in situ forming gels. As implants necessitate the use of large gauge needles (i.e., 16 gauge) or surgical procedures for administration, they are less patient-preferred (6).

Microspheres followed by in situ forming gels systems have resulted in the majority of approved peptide therapeutics and are prepared from degradable polymers such as polyanhydrides, polyesters usually from poly(lactic-co-glycolic acid), lipids such as Depofoam (Pacira) (7) and Fluid-Crystal (Camurus) (8), or even by the self-assembly of the actual endogenous peptide (e.g., lanreotide acetate [Somatuline Autogel, Ipsen]) (9) and their derivatives (usually with polyethylene glycol, poly(orthoesters), sucrose acetate isobutyrate), collagen, hyaluronic acid, and chitosan (10, 11). Nanoparticulate parenteral delivery, although still in preclinical stage, is showing promise particularly for delivery of peptides across notoriously impermeable barriers, such as the BBB (12, 13), where neuropeptides can prove significant therapies for neurological disorders (e.g., pain, depression, and neurodegenerative disorders).

Advents in injection devices enable self-administration by patients using a small-diameter needle and syringe, such as in the case of insulin. Prefilled syringes, auto-injectors, syringe injectors, pen devices, and needleless injectors contain cartridges loaded with the peptide. With the exception of needleless injectors, no further pharmacokinetic studies are required because these systems result in similar pharmacology and toxicity with equivalent bioavailability (14).

Oral peptide delivery

There are currently only two oral peptide formulations available on the market—desmopressin acetate (DDAVP, Sanofi-Aventis) approved for the treatment of diabetes insipidus, and cyclosporine (Neoral, Novartis) as an immunosuppressant (15). Both are cyclic peptides whose structural features protect them from intestinal proteolytic degradation. In the case of desmopressin, substitution of the last L-arginine by a D-arginine, and deamination of the first amino acid results in an oral bioavailability en-
The pharmaceutical industry, driven by the medical and clinical success of intravenously administered biologics, is increasingly accepting more complex brain and peptide drug-delivery systems to enter niche treatment markets and address the growing need for brain therapeutics. The translation of a technology for oral peptide delivery to the brain can provide an answer to a therapeutic field with unmet needs.

For oral to brain peptide delivery, the focus has been on delivering endogenous opioid peptides and their analogs for the treatment of neuropathic and chronic pain. The first reported strategy able to deliver peptides orally involved a leucine-enkephalin synthetic analogue (dalargin) encapsulated in polybutylcyanoacrylate nanoparticles overcoated with polysorbate 80 (32), and in some cases, overcoated with polysorbate 80 and polyethylene glycol (20 kDa) (33). However, the technology has not yet progressed into Phase I studies.

On the other hand, Nanomerics has announced that its nanotechnology-enabled peptide pill (METDoloron) involving the molecular-envelope technology (MET) will be moving into Phase I clinical trials within the next two years (34). The technology is based on an engineered amphiphilic chitosan polymer (i.e., quaternary ammonium palmitoyl glycol chitosan) tailored for Neoral (17).

The major challenge is enhancing the oral bioavailability of peptides from less than 1% (which is common for peptides) to at least 10–20%, and if possible, to 30–50% (18). The enhanced potency of peptides necessitates only minute amounts to bind to receptors. Whereas for efficacy, the low oral bioavailability requires larger doses to be administered, thereby, increasing development costs and the costs of therapies, especially if the peptide is larger than 50 amino acids and cannot be easily synthesized using solid-phase peptide synthesis. In such cases, cost constraints on healthcare providers limit their development for life-threatening and unmet diseases (19).

**Chemical modification and formulation strategies**

Strategies to enhance peptide oral bioavailability can be divided in chemical modification or formulation strategies. Chemical modification can involve substitution of natural amino acids with D-amino acids (20), cyclization (21), engineering peptidomimetics by replacing labile bonds with stable constructs (22), introduction of steric bulk (N-alkylation), or formation of a prodrug (13) to increase lipophilicity or decrease hydrogen bonding to enhance permeability across epithelial cells.

Formulation strategies for enhancing absorption across the GIT or improving peptide stability include co-administration of enzyme inhibitors (23, 24) or absorption enhancers (e.g., low molecular weight surfactants, bile salts, and cyclodextrins), altering the gastrointestinal retention time using mucoadhesive polymers such as chitosans (12, 25), and encapsulating or conjugating the peptide to a suitable lipicarrier (26) or micro/nanoparticle systems (12, 13). Despite the numerous oral peptide delivery technologies, few have progressed beyond proof of concept to human clinical trials, with most of them designed to enable oral delivery of insulin fuelled by the broad existing market (see Table I). Although the hurdle to commercial development was predicted to be safety, it appears to be study design and ensuring efficacy in humans (11).

**Nanotechnology**

Nanoparticulate technologies are receiving interest for their ability to enable oral peptide delivery to the brain. The pharmaceutical industry, driven by the medical and clinical success of intravenously administered biologics, is increasingly accepting more complex brain and peptide drug-delivery systems to enter niche treatment markets and address the growing need for brain therapeutics. The translation of a technology for oral peptide delivery to the brain can provide an answer to a therapeutic field with unmet needs.

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to form nanoscale polymeric aggregates that are able to package or specifically interact (covalently and noncovalently) with peptides (13).

Preclinical studies showed successful delivery of leucine-enkephalin across the BBB with significantly higher pharmacokinetic amounts (i.e., a 67% increase in plasma levels [AUC$_{0-24}$] and a 57% increase in brain maximum concentration [C$_{max}$]). Moreover, significant enhancement of pharmacodynamic activity in a pain animal model was observed (13). Combining the molecular-envelope technology with a prodrug lipidization strategy of leucine-enkephalin potentiated the oral antinociceptive effect, leading to analgesia lasting more than eight hours after oral administration, accompanied with significant enhancements in brain bioavailability (13).

The commercialization of peptides as oral therapies is still deemed risky by the biopharmaceutical industry. However, the reward of niche treatment market areas will fuel the development of a peptide pill enabled by nanotechnology either alone, or combined with chemical modification (lipidization, cyclization) or other formulation strategies (controlled-release polymer coating, permeation enhancers, protease inhibitors).

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A Q&A with K-Tron’s Sharon Nowak

Loss-in-weight feeders provide high accuracy for batch or continuous processes.

Bulk-solids feeders are devices that meter the flow of bulk solids (e.g., powders) from a source (e.g., storage hoppers and intermediate bulk containers) to the downstream process at a precise flow rate. The optimal feeder depends on the powder’s flow characteristics as well as the precision and throughput needed. In the pharmaceutical industry, single or twin-screw, volumetric or gravimetric feeders are commonly used to meter powders in various processes, such as milling, granulation, coating, direct compression, and blending. Pharmaceutical Technology spoke to Sharon Nowak, global business development manager for food and pharmaceutical, K-Tron, to find out more about how gravimetric, loss-in-weight feeders can be used in pharmaceutical bulk-solids processing, including their use in continuous-manufacturing processes.

Comparing volumetric and gravimetric feeders

PharmTech: How do volumetric and gravimetric feeders differ?

Nowak: Volumetric feeders control flow by metering a constant volume per time by regulating the speed of the feeding device. In the case of screw feeders, for example, this control would include setting the screw speed. The required speed is calibrated by weighing a timed sample. It should be noted that although there is no feedback to ensure feeding accuracy over time, this function may not be a concern for certain applications or materials with consistent bulk density. For this reason, volumetric feeders can be an economical choice for free-flowing materials and batch processes that require a lower degree of accuracy.

Gravimetric feeders, on the other hand, are real-time devices that meter the rate at a constant weight per unit of time. Weight is measured using a load cell; a feedback loop regulates the speed of the feeding device to control the feeder’s accuracy. Gravimetric feeders as provided by K-Tron, for example, provide a much higher degree of accuracy, typically in the range of 0.25–0.5% of the required massflow setpoint.

How a gravimetric feeder operates

PharmTech: Can you explain further how a gravimetric feeder works?

Nowak: The most popular type of gravimetric feeder used in continuous processes is the loss-in-weight feeder (see Figure 1). Loss-in-weight feeders directly measure and control the process variable of flow rate and can fully contain the material within the confines of the feeder. Loss-in-weight feeders are typically either mounted on weigh scales or suspended from load cells. The K-Tron load cell, for example, is designed specifically for the rate and accuracy requirements of dynamic feeding and includes a resolution as high as 1:4,000,000.

A loss-in-weight feeder consists of a hopper and feeder that are isolated from the process, so the entire system can be continuously weighed. As the feeder discharges material, system weight declines. The speed of the metering device is controlled to result in a per-unit-time loss of system weight equal to the desired feed rate. A typical loss-in-weight feeder controller adjusts feeder speed to produce a rate of weight loss equal to the desired feed-rate setpoint.

Any changes in material bulk density are sensed and accounted for by a
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change in metering speed. Precision, digital load cells from K-Tron, for example, use vibrating-wire weighing technology and digital filtering to discriminate between weight data and environmental effects, such as temperature, ambient vibration, and shock (Smart Force Transducer, K-Tron).

Measuring feeder accuracy
PharmTech: How is the accuracy of a gravimetric feeder determined?

Nowak: Weigh-feeder accuracy, regardless of the feeder type or design, is measured by weighing a series of timed catch-samples of material discharged from the feeder. The term ‘weigh-feeder accuracy’ refers to the combined effect of two distinct, but related, performance factors: linearity and repeatability.

Linearity, as the word implies, is a measure of the feeder’s ability to deliver, on the average, the desired flow rate throughout the feeder’s full range of operation (see Figure 2). A linearity measurement, therefore, reveals the difference between the actual and desired average sample weight at various flow settings. Repeatability, on the other hand, is a measure of the degree to which the feeder discharges a constant flow of material over a specified time period at a given flow-rate setting. Usually made at the intended nominal operating flow rate, a repeatability measurement indicates the level of scatter or dispersion (around the average sample weight) of the group of weighed catch samples. A feeder’s linearity measurement quantifies how well or poorly it delivers the desired average rate at each of various points throughout the feeder’s complete operating range. Perfect linearity is represented by a straight-line relationship between the setpoint and the actual average feed rate throughout the feeder’s specified turndown range from its design, full-scale operating range.

In addition, feeders should be designed to maintain accuracy during the refill phase, in which material is replenished in the feed hopper and the feeder is momentarily not being controlled by loss in weight. In the past, feeders were operated by a constant metering speed during refill, but because the bulk density of the material can change during refill, this often led to overfeeding. A more accurate method (Smart Refill Technology, K-Tron) stores trending data of the weight-to-speed ratio obtained while the hopper is emptying and uses this data to gradually change metering speed during refill. The speed correction allows the mass flow to remain constant during refill. Material characteristics (e.g., bulk density, particle size and shape, angle of repose, and gas permeability) and the refill hopper size also affect the refill process and its accuracy.

Using gravimetric feeders in continuous manufacturing
PharmTech: Continuous manufacturing is predicted to grow in use for solid-dosage manufacturing. What technology is needed to feed continuously?

Nowak: Gravimetric feeders are typically the technology of choice for continuous pharmaceutical processing, such as hot-melt extrusion or continuous direct compression, because the loss-in-weight controller is a real-time device that provides the accuracy needed for continuous process control. In a continuous process, the feeder sets the precise throughput for the downstream equipment, and feeding performance largely affects the performance of subsequent unit operations.

Due to the shorter residence times in continuous pharmaceutical processes, automatic sampling of feeder performance is often performed at smaller time intervals, from 15 seconds down to 5-second and even 1-second sampling. For this reason, it is imperative that the control system of the feeder chosen for continuous operations has fast response times. Although use of gravimetric feeders for continuous processing in the pharmaceutical industry is fairly new, these feeders have been an integral part of continuous processing in the food and plastics industries for decades.

Gravimetric feeders in tablet-press lubrication
PharmTech: How are gravimetric feeders used in tablet-press lubrication?

Nowak: Recently, gravimetric feeders have been used for direct, external lubrication of tablet presses, in which magnesium-stearate lubricant is blown into the press, which can reduce stearate use by as much as 97%. This significant reduction in the amount of lubricant added in the blending stage can drastically improve the blend properties, making it more free flowing as well as reducing the possibility of the formulation sticking to the tablet-press tooling. This concept was illustrated in a poster presented at an AAPS (American Association of Pharmaceutical Scientists) meeting (1). The use of a loss-in-weight feeder to control the rate of lubricant to the press allows processors to precisely measure how much is going in; by measuring how much stearate remains after processing, the amount of stearate in the formulation can be quantified (1). Typical feed rates of magnesium stearate for this application are 0.2–2 kg/h, and microfeeders allow rates as low as 50 g/h.

Reference
A Pragmatic Application of QbD: Turning Theory into Tangible Success

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E V E N T  O V E R V I E W

A well-designed Quality by Design (QbD) approach to drug development and manufacturing can substantially minimize development and scale-up challenges and increase the reliability of the manufacturing process. While a wealth of information exists on the theory behind QbD, there is no ‘one size fits all’ application of it. For a project to reap the added benefits of quality and robustness resulting from QbD, it is critical to understand how to use some of the QbD tools to identify and control the factors contributing to product variability. For example, reduced product variability from QbD can lead to cost savings as a result of decreased batch failure during routine manufacture.

During this 60-minute webcast, two industry experts will share case studies and their experience with QbD and offer insight into how the practical application of QbD contributed to the success of their projects — steps that can be universally applied to your projects.

Don Barbieri, associate director of formulation and process development, Patheon, will present case studies demonstrating different aspects of the QbD approach, including identifying CQAs (critical quality attributes) and CPPs (critical processing parameters) as well as risk assessment determination, risk mitigation, DoE, and more.

David Smith, pharmaceutical specialist, formulation and process development, Patheon, will present a case study where the pragmatic application of QbD enabled a successful tech transfer of a film-coated tablet from Phase III to commercial scale.

Key Learning Objectives:

- How a team approach impacts the success of QbD: Support and commitment of a whole team enables success and requires input from both subject matter experts and QbD experts on the team.
- How a simple approach to QbD can control variations within a manufacturing process.
- How a QbD approach to product and process development differs from more traditional approaches and can improve quality and reduce challenges.

Who Should Attend:
- Formulators
- Developers
- Quality by Design professionals
- Process developers
- Process optimizers
- Formulation scientists
- Formulation R&D managers, directors, and group leaders
- Process development scientists
- Process development managers, directors, and group leaders
- Section Heads
- Project Managers
- Technical personnel involved in quality
- Technical personnel involved in process optimization
- Technical personnel involved in formulation and development
- Scientists, manager, directors, and group leaders involved with formulation

Presenters:

David Smith
Pharmaceutical Specialist
Formulation and Process Development
Patheon

Donald Barbieri
Associate Director
Formulation and Process Development
Patheon

Moderator:

Patricia Van Arnun
Executive Editor
Pharmaceutical Technology

For questions, contact Kristen Farrell at kfarrell@advanstar.com
Solid-form characterization and research are important for improving the understanding of and modification of the physical properties of APIs to ensure therapeutic benefit, optimize product development, and protect intellectual property. Although the primary goal early in drug development is to find a stable form of the drug, the potential patentability of other solid forms offers opportunities in maintaining product exclusivity or for product-life extension. Solid-state chemistry is of growing importance not only for pharmaceutical companies, but also for contract manufacturers and specialists serving the pharmaceutical industry.

The rejection by India’s Supreme Court on Novartis’ Glivec/Gleevec (imatinib mesylate) and other recent case law raise important issues on patent strategies for solid forms.

Recent intellectual property cases
In an era of increased generic-drug competition and growth in emerging markets where intellectual property laws may differ from developed markets, strategies in solid-state chemistry are ever-more important. This issue was brought into prominence with the recent ruling against Novartis by India's Supreme Court in the company’s appeal to be granted a patent for the company’s anticancer drug, Glivec/Gleevec (imatinib mesylate) in India. Although the ruling, which was issued on Apr. 1, 2013, has broader implications for intellectual property protection and the role of innovator drugs in India’s market, it also serves as a useful example on how solid-state chemistry can play a role in building a patent estate.

At issue in the case was whether Glivec was considered an innovative product and, therefore, afforded protection under Indian patent law. Novartis had argued that the beta-crystal form of imatinib mesylate was novel and that it should be given patent protection under India law. India, which is part of the World Trade Organization, had amended its patent law in 2005 to assert that pharmaceutical companies had to prove enhanced clinical efficacy of their drugs over already patented compounds (1). In its ruling against Novartis, the Indian Supreme Court cited a 1996 patent (US Patent No. 5,521,184), which included several derivatives of N-phenyl-2-pyrimidine-amine, including imatinib, in a free-base form (2). Novartis asserted that it had first developed the methanesulfonic acid addition salt, imatinib mesylate, and later the beta-crystalline form of the salt, which had improved properties, such as flow, thermodynamic stability, and lower hygroscopicity compared with the alpha-crystal form. The India Supreme Court, however, ruled that the beta-crystalline form of imatinib failed to meet the tests of “invention” and “patentability” under Indian law (1).

Novartis had filed a Special Leave Petition with the Indian Supreme Court in 2009 challenging the denial of the Glivec beta-crystal form patent on two grounds based on Sections 3(d) and 3(b) of the Indian patent law. In addition to seeking a patent for Glivec, the company filed the case to help clarify these aspects of the patent law. “Novartis has never been granted an original patent for Glivec in India,” said Ranjit Shahani, vice-chairman and managing director, Novartis India Limited, in an Apr. 1, 2013 company’s statement. “We strongly believe that original innovation should be recognized in patents to encourage investment in medical innovation especially for unmet medical needs. We brought this case because we strongly believe patents safeguard innovation and encourage medical progress, particularly for unmet medical needs. This ruling is a setback for patients that will hinder medical progress for diseases without effective treatment options.”

The recent ruling against Novartis followed another court ruling in India against a large pharmaceutical company as it related to a solid form. In September 2012, Roche lost a case in the High Court of Delhi, where it had argued that the Indian drug producer Cipla was infringing on its patents by selling a generic version of the
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anticancer drug Tarceva (erlotinib). In its ruling, the court sided with Cipla’s contention that Tarceva is based on a different polymorph of the active ingredient erlotinib than the one Roche patented in India. Roche had attempted to patent the different polymorph, but the India court had rejected it as too similar to the patented one (3, 4).

Screening and identifying polymorphs when developing and manufacturing APIs is an ongoing challenge for pharmaceutical manufacturers.

Other cases outside of India are of interest as well. For example, in March 2013, the US Patent and Trademark Office (USPTO) rejected an appeal by Boehringer Ingelheim against its refusal to patent the mesylate salt form of the thrombin inhibitor Pradaxa (dabigatran). In its decision, the USPTO asserted that a salt form of the thrombin inhibitor Pradaxa (dabigatran). In its decision, the USPTO asserted that a salt form of the different polymorph, but patented in India. Roche had attempted to patent the different polymorph, but the India court had rejected it as too similar to the patented one (3, 4).

Technical considerations

Although intellectual property concerns play a role in the development of pharmaceutical solid forms, the rationale to use a particular solid form (e.g., salt, polymorph, or cocrystal) of an API is dictated by the target product profile and encompasses various factors, such as bioavailability, physical and chemical stability, desired dissolution properties, the impurity profile of the API, drug substance hygroscopicity, morphology, size distribution, compaction properties, and the ability to formulate the drug (6).

In the case of polymorphs, for example, screening for and identifying polymorphs when developing and manufacturing APIs is an ongoing challenge for pharmaceutical manufacturers. Polymorphism is the ability of a compound to exist in more than one crystalline structure. Polymorphs or other solid forms are identified using a polymorph study or screen (6). Different solid forms can possess different properties, including solubility, which, in turn, can affect the bioavailability of the drug.

One of the more well-chronicled examples of polymorphism occurred in ritonavir, a protease inhibitor developed by Abbott Laboratories (now AbbVie). The drug was approved in 1996, and in mid-1998, Abbott encountered manufacturing difficulties with the capsule formulation (5). Ritonavir exhibited conformational polymorphism of two unique crystal lattices that had significantly different solubility properties (6, 7). The formation of the polymorph caused Abbott to pull the drug from the market and reformulate.

Polymorph stability is evaluated experimentally by monitoring the phase transition of the different polymorphs in different crystallization media and at different temperatures by using in-situ monitoring probes and analytical solid-state methods (6). These data are used to

**Academic and public partnerships in solid-state chemistry**

Although the actual synthesis of an API is crucial, it is not the exclusive consideration in API development. In addition to producing an API with high purity, yield and stereoselectivity, an API must be able to remain stable during storage and distribution and have the desired drug mechanism once administered to a patient. Solid-state chemistry is an important part of drug development, and public research is advancing the field.

Researchers at the Institute of Chemical and Engineering Sciences (ICES) at Singapore’s Agency for Science, Technology, and Research (A*STAR) recently reported on a novel method for producing cocrystals. The researchers discovered that adding water droplets can help form cocrystals of caffeine. Caffeine is unstable to humidity and cocrystal formation is possible with biocompatible compounds such as 4-hydroxybenzoic acid (4HBA). Previous research showed that computer models could predict cocrystals of caffeine and 4HBA in the ratio of 1:1, which would be the form with the most stable structure. To date, researchers had only been able to produce 2:1 and 1:2 cocrystals, according to information from A*STAR (1).

The ICES researchers successfully formed 1:1 cocrystals of caffeine and 4HBA in the form of a monohydrate. By grinding together a 1:1 mixture of the two components with two drops of water, a crystal structure was formed in which each pair of crystallization partners is partly held together by a water molecule. The key to the water’s ability to produce the 1:1 cocrystal is its capacity to both donate and accept hydrogen bonds, the intermolecular force that holds cocrystals components together. In the case of the caffeine–4HBA cocrystal hydrate, unused hydrogen-bond acceptors and donors are satisfied by forming hydrogen bonds with the water molecule. Without water, the number of hydrogen-bond donors and acceptors is unbalanced, resulting in the preferential formation of the 2:1 and 1:2 crystals instead, according to the A*STAR information. The researchers have also applied the process to other APIs. They generated a 1:1 cocrystal hydrate of 4HBA with piracetam, a cognitive-enhancing drug. The results suggest that forming hydrates offers an alternative way to generate cocrystals with particular ratios of constituents, expanding the options for forming pharmaceutical materials.

The Synthesis & Solid State Pharmaceutical Center (SSPC) at the University of Limerick in Ireland was recently one of seven research centers that received part of an EUR 300 million ($391 million) investment through the Science Foundation Ireland’s (SFI) Research Centers Program. SFI is the national research foundation in Ireland, and the funding represents funding from both SFI and private funding from industry. SSPC is a collaboration between 17 companies and academic institutions. These groups have expertise in process modelling and design, scale-up, computational fluid dynamics, in-situ solution and solid-phase monitoring, crystallography and powder characterisation. The center’s goal is to rationally design solid-state pharmaceutical materials in the required physical and chemical forms for advanced formulation and drug-delivery systems.

Reference

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manufacture the desired polymorph and to control it through the various manufacturing steps. Polymorphs can undergo phase transitions when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray drying and compaction. Exposure to environmental conditions, such as humidity and temperature, also can induce polymorph transition. The extent of transition depends on the relative stability of the polymorphs, kinetic barriers to phase transition, and applied stress (6). Moreover, the physical stability of polymorphs may be monotropic or enantiotropic, where the relative thermodynamic stability between the two forms can be inverted with temperature (6). Additional considerations are made when stabilizing particular physical and other process parameters that may affect the performance or quality of the product.

Different solid forms can possess different properties, including solubility, which, in turn, can affect the bioavailability of the drug.

Cocrystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Cocrystals are used to improve the performance of APIs that have non-ideal physiochemical properties by cocrystallizing the API with a second compound that modulates the API to provide a way to improve a drug’s bioavailability, stability, and processability. Cocrystals, however, are different from traditional pharmaceutical solid-state forms. Unlike polymorphs, which generally contain only the API within the crystal lattice, cocrystals are composed of an API with a neutral guest compound conformer in the crystal lattice (1). Unlike a salt form where the components in the crystal lattice are in an ionized state, the molecules in the cocrystal are in a neutral state and interact by means of nonionic interaction, thereby providing a way to produce solid-state forms even for APIs that lack ionizable functional groups needed for salt formation (1).

Researchers at the University College London (UCL) and the University of Bradford in the United Kingdom recently reported on the use of thermal ink-jet (TIJ) printing technology to produce pharmaceutical cocrystals. The researchers identified cocrystals in all cases where the coformers could be dissolved in water or mixtures of ethanol and water as the solvents because other organic solvents may react with the plastic cartridges of the printer (3).

The research was led by Simon Gaisford, reader in pharmaceutics at the UCL School of Pharmacy, whose research is focused on using TIJ technology to produce pharmaceutical forms. Instead of using ink in a print cartridge, the ink is removed and replaced with a drug solution. A TU system consists of a reservoir of liquid to be jetted mounted above a printhead. The printhead, usually produced with photolithography, consists of a number of small chambers, filled with liquid from the reservoir, each in contact with a resistive element. Pulsing a current through the element results in a rapid rise in temperature, causing evaporation of some of the liquid, nucleation and then expansion of a vapor bubble. As the bubble expands, some liquid is ejected from the chamber, forming a droplet. The fine control of liquid deposition can be used for pharmaceutical applications (4).

Other applications of TUJ technology from Gaisford’s research have included making personalized-dose oral films of salbutamol sulfate by replacing the paper in the printer with a sheet of polymer film that allowed the drug to be jetted onto the surface (4). A printer cartridge was modified so that aqueous drug solutions replaced the ink (5). The film strips were cut. Varying the concentration of drug solution, area printed or number of print passes allowed the dose to be controlled (4, 5). The print solution viscosity and surface tension were used to determine the performance of the printer. A calibration curve for salbutamol sulfate was prepared, which showed that drug deposition onto an acetate film varied linearly with concentration. The printer was then used to deposit salbutamol sulfate onto an oral film made of potato starch. The researchers found that when doses were deposited in a single pass under the print head, the measured dose was in good agreement with the theoretical dose. With multiple passes, the measured dose was always significantly less than the theoretical dose (5). The researchers surmised that the losses result from the printed layer eroding by shearing forces during paper handling.

References
1. Indian Supreme Court, Civil Appeal No. 2728 Novartis AG vs. Union of India and Others (Mumbai, 2013).
EVENT OVERVIEW:
USP standards for the identity, strength, quality, and purity of medicines are an integral part of drug development and manufacturing. Modernization of USP monographs and development and revisions to General Chapters is a top priority for the USP Pharmacopeial Convention in 2013. Learn from USP experts of the status and progress of these efforts, Monograph Modernization progress, New General Chapter content for Excipients, Analysis of Elemental Impurities, Microbiology, and the Medicines Compendium (MC).

Speaker:
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Moderator:
Patricia Van Arnum
Executive Editor Pharmaceutical Technology
Enhancing Particle-Size Measurement Using Dry Laser-Diffraction Particle-Size Analysis

Carl Levoguer

Across the pharmaceutical industry, laser-diffraction technology is well established for particle-size measurement. Laser diffraction is an efficient method of particle sizing and lends itself to automation as evidenced by the ready availability of highly automated laboratory instruments and real-time sizing technology for pilot and commercial scale applications. Ongoing advancement of the technique offers considerable benefits to the pharmaceutical industry with recent extensions of the application of dry-powder measurement an especially useful innovation.

Although dry particle-size measurement is particularly beneficial for moisture-sensitive materials, it also offers wider efficiency and environmental advantages. Maximizing the use of dry measurement enhances instrument productivity through rapid measurement and cleaning while at the same time minimizing the waste-disposal issues associated with the use of dispersants in wet measurement. Dry measurement, however, relies on being able to efficiently disperse the sample, without causing particle damage, in order to access accurate primary particle-size data. This dry dispersion can be particularly challenging for some of the fine and fragile materials routinely handled by pharmaceutical manufacturers.

In this article, the author contrasts the benefits and limitations of wet- and dry-sample preparation by focusing on the benefits of dry dispersion. The mechanisms that give rise to agglomerate break-up are discussed with reference to different designs of the dispersion unit, and experimental data are presented to show the suitability of different dispersion environments for different types of material.

Preparing samples for particle-size measurement

One of the attractions of laser-diffraction particle-size measurement is that sample-preparation requirements are minimal. That said, it is vital that the particle-size data measured are fully relevant to the application. In some instances, it is the size of particles present in the raw sample that is of interest perhaps because of the need to investigate process performance or to evaluate the agglomeration of a fine material during storage. More usually, however, it is the need for primary particle-size data that drives analysis because particle size defines important attributes such as solubility and bioavailability. This requirement makes it essential to disperse the sample prior to measurement, to break up any agglomerates or aggregates.
present and ensure that discrete particles are reliably introduced into the measurement zone of the instrument. There are two possible approaches: wet or dry dispersion.

Wet measurement involves the production of a stable suspension using a suitable dispersant. The choice of dispersant will depend upon the solubility of the material to be analyzed; therefore, water-soluble materials often require a suitable organic dispersant. Ultrasound is often applied, in combination with defined levels of agitation, to achieve a homogeneous suspension, and in some instances, additives also will be required for stabilization and wetting. The most advanced laser-diffraction instruments allow wet measurements to be made on very fine powders with particle-size distributions extending down to 0.01 micron in size.

The dispersion mechanisms applied in wet measurement, although effective, are relatively gentle, which means wet measurement can be successfully used for even the finest and most fragile of particles. Wet dispersion is useful for establishing a baseline against which the success of dry dispersion can be judged. The less appealing aspects of wet measurement are that it takes longer than the dry alternative and produces waste in the form of used dispersants and additives. The time required and the production of waste are particularly drawbacks for polydispersed samples, where the volume of sample must be large to ensure representative data for every size fraction.

With the latest laser-diffraction instrumentation, dry-powder dispersion can be applied to materials in the particle-size range 0.1 to 3500 microns. The widest possible use of dry dispersion maximizes the productivity of a laser-diffraction analyzer, simultaneously minimizing environmental impact. The challenge, however, is to apply sufficient energy to deagglomerate the sample without causing primary particle damage. Using dry measurement, the sample is dispersed into a compressed air flow. Increasing the pressure of this air makes the dispersion process more energetic, but the design of the disperser...
Particle-Size Analysis

Figure 2: Pressure-titration data for a lactose formulation shows close agreement between the wet (blue) and dry measurement obtained with a compressed air pressure of 3 bar with (a) the standard venturi (upper plot) and at 1 bar with (b) the more aggressive venturi (lower plot). US refers to after ultrasound; HE refers to high energy.

Figure 3: Comparing pressure-titration data for the two venturis shows that the standard, less energetic design offers more robust measurement and a working pressure envelope that extends from 3 to 4 bar. DV50 is the median particle size based on a volumetric particle-size distribution.

is crucial in defining the aggressiveness of the dispersive action. The breadth of samples for which dry measurement is feasible with a given particle-size analyzer, therefore, directly depends on the design of the dry disperser.

Understanding the mechanisms of dry dispersion
The interparticle forces that bind particles together include van der Waals forces, electrostatics, and liquid bonds. As particle size decreases these forces become stronger, thereby making dispersion tougher for finer materials. In dry dispersion, the mechanisms that can be applied are, in order of aggressiveness:

- velocity gradients caused by shear stress
- particle to particle collisions
- particle to wall collisions.

The design of the disperser used dictates which mechanism is applied during measurement. The disperser geometry shown in Figure 1 (a), for example, has no impaction surfaces. As sample drops down from the sample tray into the funnel, it is entrained into the compressed air, which enters at right angles to the powder. Dispersion is achieved by accelerating the particles through the venturi
into the measurement zone through the application of shear and as a result of particle–particle collisions. This design is, therefore, suitable for relatively fragile particles.

In the alternative, high-energy venturi shown in Figure 1(b) the inclusion of a 90-degree bend creates an effective impaction zone that brings the third dispersion mechanism into play. For highly cohesive materials, this impaction is a useful strategy, but only if the particles are sufficiently robust to withstand the applied forces.

The latest laser-diffraction systems (e.g., Mastersizer 3000, Malvern Instruments) offer multiple dispersion-configuration options that streamline the use of different geometries to allow users to apply alternative set-ups for different materials. By simultaneously enabling precise control of the powder-feed rate and the pressure of the compressed air, such systems enable the manipulation of dispersion to achieve robust dry measurement for a wide range of sample types as illustrated in the following case study.

**Case study: Identifying an optimal dry dispersion method for a lactose-based formulation**

In an experiment to identify the optimal method for the dry measurement of a lactose-based formulation, various tests were carried out using a dry-dispersion engine (Aero S, Malvern Instruments) of a laser-diffraction system (Mastersizer 3000, Malvern Instruments), which can be configured with either a standard (see Figure 1(a)) or a high-energy (see Figure 1(b)) venturi geometry. With both dispersers, a standard pressure titration was carried out; that is particle size was measured as a function of the pressure of the compressed air used for dispersion. In addition, a wet dispersion of the formulation was measured to set a baseline for the evaluation of dry methods.

Figure 2 shows the pressure-titration results for both venturis with data sets overlaid for dry and wet measurement. These results indicate that with the standard design, agglomerates are still present at air pressures in the region of 0.5 to 1 bar. A pressure of 3 bar is required for complete dispersion and to achieve close agreement between the wet and dry data.

Analogous data for the high-energy venturi reflect the more aggressive nature of the dispersion mechanisms applied and show close agreement between the wet and dry results at an air pressure of approximately 1 bar. At higher pressures, there is evidence of primary particle breakdown with the reported particle size becoming smaller than that measured using the wet method.

These data suggest that either disperser could be chosen for analysis of the formulation provided that an appropriate air pressure was selected, but this conclusion raises a question: Are both dispersers equally suitable for this application or is one more appropriate than the other?

By examining how Dv50 (i.e., the median particle size based on a volumetric particle-size distribution) changes as a function of applied air pressure (see Figure 3), it is possible to identify the standard, less energetic venturi as the better choice. With the high-energy venturi, although the results match with wet measurement at 1 bar, any variation in pressure, to either side of that figure, produces a mismatch between dry and wet data. This mismatch suggests that the measurement result will be sensitive to slight variations in air pressure and that the method is not inherently robust.

In contrast, with the standard venturi, particle size is stable across a 1-bar pressure window, from 3 to 4 bar. This greater stability indicates that measurement with the standard venturi will be inherently more robust and that less aggressive dispersion is preferable for this relatively fragile powder.

**Conclusion**

Recent advances in laser-diffraction particle-sizing instrumentation have extended the measurement range of the technique, extending up to 3500 microns, and significantly improved the ease of use of these systems, a key determinant of general laboratory productivity. Equally importantly, however, recent instruments have brought enhanced dry-powder dispersion capability. Relative to wet measurement, dry-laser diffraction particle-size analysis is faster and has a lower environmental footprint because no dispersants are required. Developments in this area, therefore, offer significant practical benefit.

The latest laser-diffraction systems have dry-dispersion engines with a choice of disperser geometries, backed up with precise control, both of sample feed rate and the pressure of the compressed air used for dispersion. Such systems allow the user to control the mechanisms applied to disperse the sample, and most crucially, to efficiently disperse samples without impaction, where impaction must be avoided. As a result, modern laser-diffraction systems extend robust dry measurement to a wide range of sample types, including to materials that are both cohesive and relatively fragile. Such advances mark an important step forward that further enhances the suitability of laser diffraction for efficient particle-size measurement.
Understanding ICH Q11—FDA’s Guidance on the Development and Manufacture of Drug Substances

Bob Mehta


In November of 2012, FDA issued Q11 Development and Manufacture of Drug Substances (1). The International Conference on Harmonization (ICH) Q11 Expert Working Group developed the FDA guidance (1). Additionally, the term “guidance” is a reflection of the agency’s current thinking on this topic and should be considered as nonbinding recommendations only. Current FDA regulations for GMPs do not cover APIs specifically, so the adoption of ICH Q11 as a guidance document was deemed to be a reasonable approach by the agency. In accordance with this guidance, manufacturers can use alternate approaches needed in the development of drug substances. Q11, however, delineates two viable approaches for drug-substance development: traditional and enhanced (2). The traditional approach is premised on establishing set points and specific operating ranges for all process parameters (2). The control strategy for drug substances is predicated on process reproducibility and repeatability and the implementation of an effective program for drug-substance testing against predefined criteria. The enhanced approach entails the employment of risk-management strategies and the application of scientific knowledge to garner a better understanding of process parameters (2). The concept is to develop and implement control strategies and then employ these strategies over the drug-substance lifecycle to support a better understanding of critical quality attributes (CQA) needed to produce safe drug substances and the establishment of design space (as applicable).

To enhance the understanding of Guidance for Industry: Q11 Development and Manufacture of Drug Substances, it is important to have some basic knowledge of ICH and the interrelationship of guidelines published by ICH. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use was founded in 1990. Pharmaceutical industry regulators from the United States, Japan, and Europe were brought together for the succinct purpose of improving global harmonization of regulatory requirements needed to support the design and development for medicines that are safe and effective in their intended use (3). Guidelines
developed by ICH Expert Working Groups are divided into four categories: quality guidelines, efficacy guidelines, multidisciplinary guidelines, and safety guidelines (3). Several countries have adopted ICH guidelines as law; however, FDA only considers the guidelines as guidance. Implementation of the guidance provided in Q11 requires knowledge of applicable ICH guidelines referenced specifically in of Guidance for Industry: Q11 Development and Manufacture of Drug Substances.

**Manufacturing process development**
One of the requirements needed for the manufacturer of quality drug substances are validated processes capable of providing repeatable results. In support of accomplishing the task of manufacturing a quality product, manufacturing process development requires adherence with six quality principles delineated within Q11:
- Drug-substance quality linked to drug product
- Process-development tools
- Approaches to development
- Drug-substance CQAs
- Linking material attributes and process parameters to drug substance CQAs
- Design space (1).

Manufacturers are expected to understand the impact of raw-material attributes on drug substances (e.g., CQAs). Additionally, the expectation is that quality risk management (QRM) tools be employed wherever possible (4). Furthermore, manufacturers should focus on the design and development of a fundamentally sound approach for drug development. As delineated in the introduction, a traditional or enhanced approach can be employed or a combination for the two for drug-substance development. It should be noted that the traditional approach has been the preferred method of drug development for years. Q11 and FDA’s guidance allows for some flexibility so manufacturers can implement a system that works for them. There are, however, specific elements that need to be implemented: identifying all CQAs, defining the manufacturing process, and defining and implementing a control strategy.

Finally, the identification of CQAs and understanding the influence certain material attributes exude on the manufacturing process should be considered a crucial aspect of the process. This is the area where implementing a control strategy and employing QRM becomes essential; and the concept of design space is introduced into the manufacturing equation. According to Q11, design space is the multidimensional combination and interaction of two elements: input variables and process parameters (1). Design space (as defined by the manufacturer) is subject to regulatory oversight by FDA. ICH Q8 (2.4) provides additional detail on the topic of design space.

**The submission process for the enhanced approach: document requirements.** There are mandatory submission requirements in support of manufacturing process development that must be considered by drug-substance manufacturers. The submission must contain sufficient detail to support the claim for product safety and efficacy needed for eventual commercialization. For example, the expectation is that the following documentation be included as part of the drug-substance submission:
- An overall summary of the development process including: CQAs; description of design stages; description of material attributes; description of process parameters; and description and development of design spaces should be provided.
- CQAs of the drug substance shall be listed.
- A detailed discussion of the manufacturing process history needs to be provided.
- Manufacturing development studies, including risk assessments employed in support of commercial development, including the control strategy, must be provided.

**Description of process and process controls employed in manufacturing.** It is imperative that the manufacturers of drug substances provide a detailed description of the manufacturing process and the processing controls employed. The most efficient way to adequate delineate processes is through the creation of flow charts. Flow charts are an inherent requirement, regardless of submission type. In fact, Q11 requires that a flow chart be provided as part of the submission process.

**Material-selection process**
In support of the development and manufacture of drug substances, it is imperative that the quality and physical properties of starting and source materials (note: there is no difference in source versus the starting materials the vernacular used varies by region) be understood (1). Similar to manufacturing process-development requirements, the selection of starting and source materials is also premised on adherence with applicable principles. Principles associated with the material selection process, as delineated within Section 5.1 of Q11 are:
- Selection of starting materials for synthetic drug substances
- Selection of starting materials for semisynthetic drug substances
- The selection of source and starting materials for biotechnical/biological drug substances (1).

Drug substance manufacturers must implement a QRM strategy. Effective implementation of QRM will result in a better understanding of risk and the link between risk and the number of process steps. Also needing to be considered are drug-substance material properties and the management of drug impurities (1). According to Q11, regulatory authorities will assess the controls employed by manufacturers, “including those needed how impurities are formed in the process; how changes in the process could affect the formation, fate, and purge of impurities” (1).
ICH Q11: Drug Substances

As a point of reference, ICH Q7 is an excellent starting point when it comes to understanding the need for the employment of GMPs needed for managing starting materials (5). Application of ICH 7 has become mandatory in some ICH regions (e.g., the European Union). It should be noted that unlike reagents, starting material should be considered a significant structural fragment of the drug substance. Similar to synthetic drug substances, semisynthetic drug substance starting materials must be understood and adequately described (e.g., “chemical synthesis and elements of biological origin” (1)). When considering the selection of raw materials for biotechnological/biological drug substances, manufacturers should apply the ICH 5 series (6-10) of guidance documents (6).

Submission of relevant information. In support of the submission process, manufacturers are required to provide a list of the raw materials being used and their specifications, supported by written justification as to why these materials are acceptable. This justification is required for synthetic, semisynthetic, and biotechnological/biological drug substances.

Control strategy
A control strategy is the development and implementation of adequate controls to ensure the continued repeatability of process performance and the ongoing assurance of finished product quality. The control strategy and subsequent control steps implemented are premised on a thorough understanding of manufacturing processes, the expected behavioral characteristics of raw materials, and sources of variability associated with a CQA (1). Elements of an effective control strategy typically include:

- Controls employed for raw materials
- Controls associated with the design manufacturing process
- In-process controls (i.e., testing and process control points)
- Controls placed on the drug substance (e.g., release testing) (1).

Submission of relevant information. In support of the submission process, the control strategy employed must be provided in sufficient detail that includes a detailed description for each of the control-strategy elements. The information can be depicted in a table or through the use of a visual aid (e.g., flow chart delineating control points). As a minimum, the following control-strategy plan elements should be included in the submission:

- Description of manufacturing-process controls
- Controls employed for materials
- Controls for identified critical process steps
- Controls for the drug substance
- Container closure systems (5).

Process validation
It is a fundamental expectation that manufacturers of drug substances validate their processes as appropriate. From an ICH perspective, process validation is “the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes” (1). The targeted result of process validation is the collection of scientific evidence to support claims that a process is stable and capable of providing a predictable and repeatable output. Validation activities are expected to be pursued from initial drug-substance design through to the processes employed for manufacturing, including packaging.

Employing the CTD format for information submission
Drug substance quality, safety, and efficacy data must be compiled and placed into the Common Technical Document (CTD) format. Additional guidance pertaining to FDA’s requirement for electronic submissions can be found in Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications And Related Submissions Using the eCTD Specifications (11). According to ICH M4, the CTD is broken down into four modules (note: the first bulleted point is not part of the CTD):

- Module 1—Region-Specific Information
- Module 2—Quality and overall summary and clinical overview and summary
- Module 3—Quality
- Module 4—Nonclinical study reports
- Module 5—Clinical-study reports (12-16).

According to FDA’s guidance, organization of the electronic submission should be in folders that align with Modules 2 through 5 (11).

Lifecycle management
ICH Q11 requires the manufacturers of drug substances to implement continuous-improvement practices throughout the entire lifecycle of each drug substance. The employment of science and risk-based approaches for each lifecycle stage is a fundamental expectation of the ICH Q11 Guidance Document (1). A true lifecycle will encompass all stages from initial design and development, validation of processes, manufacturing, commercialization, and end-of-life. Manufacturers are expected to evaluate manufacturing processes, the control strategy, and ongoing product safety and efficacy. All knowledge garnered during these evaluations, including knowledge gained from post-market surveillance activities, should be used to drive ongoing product improvement. Additionally, information collected should include:

- Process-development activities
- Technology-transfer activities
- Process-validation studies
- Change-management activities (1).
EVENT OVERVIEW
All pharmaceutical manufacturers are required to comply with regulations for cleaning validation. Many companies have incorporated their historical practices with limited scientific underpinning and little evaluation of risk. Some companies have chosen to avoid the debate entirely by using expensive disposable systems exclusively. Using the latitude available in cGMPs for 21st century, scientific data evaluation, and risk-based approaches can streamline the process. By developing sound and defensible programs with rapid and specific testing, cleaning validation can be efficiently and effectively implemented. This webcast will:

- Introduce the science-driven risk-based guide for cleaning validation being developed by ISPE;
- Discuss practical considerations for implementing cleaning validation programs; and
- Highlight the speed and efficiency benefits of LC/MS for development and execution of cleaning test methods.

Key Learning Objectives:
- Understand a pragmatic, science-driven risk-based approach to cleaning validation
- Gain an appreciation for considerations being development in the ISPE Cleaning Guide
- Explore the use of LC/MS for testing of cleaning samples

Who Should Attend:
- Process engineers engaged in scale-up and execution of formulation manufacturing
- Formulation development scientists involved with establishment of solid and sterile formulations
- Analytical scientists supporting cleaning validation programs
- Quality assurance staff charged with regulatory compliance of cleaning validation programs

Presenters:
Andrew Walsh, Industry Professor
Stevens Institute of Technology

Geoff Carr, Ph.D.
Director, Analytical Development
Patheon Inc.

Moderator:
Rita Peters
Editorial Director
Pharmaceutical Technology

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For questions, contact Kristen Farrell at kfarrell@advanstar.com
ICH Q11: Drug Substances

Summary
In summary, FDA’s guidance for industry, premised on ICH Q11, provides a blueprint for drug-substance manufacturers to follow when preparing a submission as part of the drug-substance application process, regardless whether a traditional or enhanced approach to design and development is pursued. It is imperative that subsidiary ICH and FDA guidance documents be reviewed and understood as these documents provide relevant information required as part of the drug-substance submission process. Fundamental requirements needing to be described, in sufficient detail, in support of the submission process are design and development, manufacturing processes, control strategy, use of starting materials, CQAs, approach to QRM, design space, and approach to continuous improvement. In closing, the CTD format has become the prescribed submission format for regulatory authorities. Ensuring that all of the technical data (i.e., quality, safety, and efficacy) required by the CTD format is organized by specific module will hopefully facilitate an orderly and efficient review of the drug substance application by the appropriate regulatory body.

References
2. ICH, Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/biological Entities) (May 2012).

Report from Brazil — contin. from page 34

ingredients already existing in the country and drugs in new pharmaceutical forms (category V) had a difference of 38% between the final price and the price requested by the industry. Other pharmaceutical products that could not be included in any category established by the government had their prices “reduced” by an average of 35% and 45%.

For products carrying innovative molecules patented in Brazil and those that have been proven to offer therapeutic benefits compared with drugs already being applied for the same use (category I), the study showed that the final cap-price was on average 19% lower than the value requested by the pharmaceutical industry, Anvisa stated. Other new products that were not patented in the country, or that had not been proven to offer therapeutic benefits (category II), had a reduction of 37% on average compared with the original price suggested.

Study details
Of all the pharmaceutical drugs studied, 45.03% were category II products. New associations of active ingredients already existing in the country and drugs in new pharmaceutical forms (category V) made up 36.72% of all products analyzed. Drugs carrying innovative molecules patented in Brazil and that have been proven to offer therapeutic benefits compared with drugs already being applied for the same use totaled to only 3.24% of all drugs studied. The other “unclassified” categories totaled to 15.01%, according to Anvisa. A relevant aspect of the study was on the number of foreign companies and Brazilian firms that were granted pharmaceutical authorizations by Anvisa for drugs carrying new molecules. According to data from the study, foreign capital firms represented nearly 82% of the total number of companies that had authorizations issued under categories I or II. However, the study showed that there were no domestic companies offering pharmaceutical drugs under category I.

Anvisa’s original study is available at http://s.anvisa.gov.br/wps/s/r/b3ZE. PT

The study evaluated the prices of pharmaceutical products containing new molecules, drugs to be sold in new pharmaceutical forms, and new associations for known active ingredients.

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

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Minimizing Out-of-Specification (OOS) Errors Using a Risk-based Gravimetric Approach

**LIVE WEBCAST:**
Wednesday, May 22, 2013 at 11:00 EST, 15:00 UTC (GMT), 16:00 BST
Register Free at www.pharmtech.com/minimizingOOS

**EVENT OVERVIEW**
Out-of-specification (OOS) errors are a major concern within analytical and QA/QC laboratories in the pharmaceutical industry because of the time and resources required to investigate the source of the problem. Fifty percent of OOS errors can be attributed to either sample preparation steps or operator error. Confidence in analytical results begins with accurate weighing because errors in the first step will have a knock-on effect. Determining the risk within a process, respecting the minimum weight, and applying the appropriate safety factor during the weighing step can address most of the weighing errors. Error-prone manual steps, undertaken during preparation of a specific concentration of solution, especially those involving volumetric glassware, can easily be replaced by the more accurate gravimetric equivalent. In addition, automation has the potential to eliminate user variability.

This 60-minute webcast will explain how to use an automated gravimetric approach to improve sample preparation workflows by offering insight from leading industry experts, including Dr. Charles Ray, former Associate Director of Analytical R&D at Bristol-Myers Squibb, who will share his practical experience in managing analytical workflows.

**Who Should Attend:**
- QA/QC Managers, Directors, and Department Heads
- Analytical Laboratory Managers, Directors, and Department Heads
- Compliance Managers, Regulatory Affairs Managers, and Global Metrology Managers
- GMP and CMC Consultants, GLP Auditors, and Quality Consultants
- Laboratory Managers, Laboratory Supervisors, and Production Managers

**Key Learning Objectives:**
- Learn how to identify and address the potential errors in manual weighing and sample preparation steps to avoid out-of-specification (OOS) results
- Understand how to use a risk-based approach to have confidence in your weighing results
- Discover how automated gravimetric methods reduce the variability and number of steps in the sample preparation process as well as provide substance savings

**Presenters**
- **Charles Ray, PhD, MBA**
  Former Associate Director of Analytical R&D
  Bristol-Myers Squibb
- **Klaus Fritsch, PhD**
  Manager Compliance,
  Laboratory & Weighing Technologies
  Mettler Toledo AG
- **Joanne Ratclif, PhD**
  Communications Project Manager,
  Laboratory & Weighing Technologies
  Mettler Toledo AG

**Moderator:**
- **Patricia Van Arnum**
  Executive Editor
  Pharmaceutical Technology

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

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Compositing involves taking samples from only one portion of units or containers, combining or blending the samples together to form a composite, and then taking a single sample from the composite and testing it once. The classic example of compositing is the receipt of, for example, 100 containers of powder. Rather than test all 100 containers, companies want to sample a few containers, mix material from several containers together, and perform only one test. Clearly, this type of sampling loses information about variability because compositing is physical averaging. The usual reason to do a composite sample is to save the cost of sampling, testing, and documentation: not a statement FDA wants to hear. The agency’s response would simply be, “That is the cost of compliance.” From a regulatory point of view, there is a need to justify compositing versus testing all of the containers on some grounds other than just cost. This testing is probably best done using statistical arguments that the composite test is sufficient in the specific situation, that additional testing would not materially improve results, or decrease patient risk.

### Compositing risks

Consideration of compositing raises several related topics. First, compositing is only done on incoming materials and not on in-process materials or on finished products. Second, compositing should not be done on crucial materials, precursors, APIs, anything that comes in direct contact with the API, in-process materials, or the finished product. The risk is too great. The probability may be low, but the consequence could be lethal to the patient if product quality is not met.

The first justification for compositing is that the risk to the patient is not materially increased by compositing. This justification is supported by the physical situation. Incoming materials generally include liquids, viscous liquids, pastes and emulsions, suspensions, powders, granulations, and solids. The nature of the material affects the sources and structure of the variability.

Take for example a tank car full of a nonviscous liquid. Generally, it is reasonable to assume that the liquid is homogeneous and one sample would be all that is needed. Thirty samples would not give more information about the liquid. The variability in the results would be from the test method itself. Now, suppose the tank car of liquid is contaminated with a heavier liquid that settles in the lowest point of the tank, usually the drain opening. If the single sample is taken from the top part of the tank, we would miss the contamination at the bottom. The sampling scheme must take into account the physical structure of the material and sources of variability.

The most common situation for compositing is the receipt of shipment of drums of a powder. A company wants to open as few of the containers as possible to take samples. The receiving company wants to mix those few samples into a blend and test one sample once. Clearly, all information about variability is lost. Further, if one of the samples that is taken and blended is low (or high) and out of specification, the blend may not be low (or high) enough to signal a difference. Again, the risk to product quality could be high.

Given 100 containers of a powder, many sources of variability can be identified within and between containers. Further, there are issues of deliberate fraud and counterfeit materials that add to possible variability. For example, drums may be filled with a cheap material such as lactose, and then only a small layer of API is put on the top. The common practice of only sampling from the top of the drum misses the lactose.

### Sampling must be supported by data, facts, and documentation.

Compositing samples is appropriate under certain circumstances but raises caveats on how and when it should be applied.

Lynn D. Torbeck


Continued on page 73
The Parenteral Drug Association presents the...

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Co-Opetition in Drug Development

Ed Currie

The author suggests co-opetition as a future model for collaboration in drug development.

Despite the looming threat of shrinking drug pipelines, drug development during the past few years has not been as productive as it should be, which has left many pharmaceutical companies at risk. To combat this issue, pharmaceutical companies are partnering with third parties, such as contract service providers, universities, and not-for-profit organizations to consolidate development processes, drive down costs, and increase output. This strategy is not as simple as it sounds, and issues, such as confidentiality and ownership, can be challenging. When handled properly, however, cross-company collaboration can result in a more efficient and profitable use of data and staff.

Industry motivations

In an industry where developing one efficacious drug can take more than 12 years, cost $1 billion in laboratory and clinical research, and has a 95% chance of failure, making the right strategic decisions to maximize the quantity and quality of new compounds is paramount.

Pharmaceutical companies not only complete with their end-products (drugs), but also in processes and technologies. In the thrust to become leaders in drug development, companies have turned to external specialists for help. This strategy has been effective, but it has led to a leveling of the playing field. CROs have been given an increasing proportion of clinical trial and regulatory activities, often managing the entire clinical process for a drug, or even all drugs of a given company. In turn, consulting and system integration firms have been hired to help optimize processes and implement large clinical, regulatory, and management systems, such as enterprise resource planning systems, with the goal of bringing drugs to market more quickly and at lower cost.

Member companies may find it difficult adjusting to collaborative models.

This experience has resulted in a relatively small number of top-tier CROs and consulting firms that have implemented systems from a small and consolidating roster of IT companies. Pharmaceutical companies are becoming similarly “best in class” in process, technology, and offshoring and outsourcing resources.

Pharmaceutical companies acknowledge that they share the same issues with respect to patent expiries, high R&D costs, and suboptimal R&D output and, therefore, should collaborate to mitigate these challenges. This realization has introduced the concept of precompetitive collaboration or “co-opetition,” whereby pharmaceutical companies parter with each other or with academia.

Co-opetition across the globe

One of the first initiatives of this type, the Clinical Data Interchange Standards Consortium (CDISC), was set up in 2000 by 32 global companies, as an open, multidisciplinary, nonprofit organization. Now with more than 200 members, it has established open standards to support the electronic acquisition, exchange, submission, and archive of clinical research data and metadata. This standardization has helped to make pharmaceutical R&D and regulatory approval more efficient by allowing collaboration among researchers, easier review of product applications by regulatory authorities, and development of clinical and regulatory software by vendors.

Regulatory authorities, such as FDA and its European and Japanese counterparts, the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency of Japan, have also been early drivers of collaborative projects. Following publication of FDA’s “Critical Path Initiative,” (1) the Critical Path Institute (C-Path) was formed in 2005 as a public–private partnership between regulators and the medical-product industry. The aim was to accelerate the pace and reduce the costs by creating precompetitive standards for data, measurement, and methods for evaluating drug efficacy and safety. In October 2012, CDISC, C-Path, and FDA formed the Coalition for Accelerating Standards and Therapies (CFAST) to work with pharma and IT companies on developing and maintaining data standards tailored to individual diseases and therapeutic areas.

In September 2012, 10 pharmaceutical companies founded TransCelerate BioPharma as a nonprofit, precompetitive drug company, to develop shared industry clinical-trial solutions (2). Such collaborative initiatives offer potential benefit to the whole industry in terms of cost and productivity. Member com-

Ed Currie is associate vice-president in the life sciences practice at Infosys in Basel, Switzerland.
edward.currie@infosys.com.
companies may find it difficult adjusting to collaborative models and may initially be hesitant to share insights that could help competitors get to market faster. Companies with healthier product pipelines might also be less willing to collaborate with those with leaner ones. The gains to all companies, however, are likely to outweigh any perceived drawbacks.

**Drug repurposing: tapping academia for new ideas**

Another area of burgeoning collaboration is between pharma companies and academic organizations, companies are looking for alternative uses for failed or unexploited compounds. To get fresh ideas from the outside, they are enlisting the help of academia.

To this end, Roche has allied with the Broad Institute of Massachusetts Institute of Technology (MIT)/Harvard, and AstraZeneca with the UK’s Medical Research Council. In another example, 10 pharma companies are partnering with the National Institutes of Health’s (NIH) National Center for Advancing Translational Sciences (NCATS) on discovering new therapeutic uses for existing molecules. An earlier-stage program recently launched in Europe under the Innovative Medicines Initiative, with seven pharmaceutical companies pooling compounds from in-house libraries.

**Viiv Healthcare: collaboration to address a single disease**

In a different model, GlaxoSmithKline and Pfizer founded Viiv Healthcare in 2009 as a commercial enterprise to focus on delivering advances in HIV treatment. Shionogi joined in 2012. Such a construction combines the complementary capabilities and pipelines of the member companies to deliver the financial strength and global reach to invest in the development of new HIV medicines. As with any joint venture, there are many details that must be agreed on contract and in spirit, for example assigning the initial and future value to each company’s portfolio, agreeing to the proportion of equity ownership, and accounting for revenues and investments.

**Further co-opetition opportunities**

If an activity affects the whole pharma industry but does not lead directly to the creation of a new molecule that is differentiated in efficacy, safety, and cost-effectiveness, that activity is a candidate for co-opetition. For this co-opetition to be truly successful, pharma companies will need to be willing to share more than they might have felt comfortable doing in the past while defining good workable contractual frameworks to govern these new relationships with each other and with third parties.

If they can achieve this model successfully, and patient confidentiality and data protection between parties are ensured, we could expect new collaborations to form in more commercially sensitive areas, such as regulatory submission and compliance frameworks, genomic-data analysis, and sales and marketing.

Reference

**Statistical Solutions** – contin. from page 70

**Skip-lot and skip-test sampling**

Another practice that companies want to do is to do “skip-lot sampling” and literally skip sampling and testing some lots. Given the necessary assumptions, skip-lot testing could be supported statistically but not from a practical point. Again, the risk to product quality is too high.

In Europe, the regulatory agencies require at least an identity test on every drum or container received. That is good practice. That requirement should be expanded to specify that some samples from the middle and bottom of some containers should be taken, and not just samples from the top.

In the past, the industry has tried to argue for “skip-test sampling”, meaning that each incoming lot of materials would be tested for identity but some lots would be skipped for a full battery of tests. Again, this type of sampling increases the risk to product quality and, therefore, the patient.

So, how to address this issue? As noted previously, a case needs to be built for compositing that does not include cost savings. This case would include how well do we know the supplier, what historical data can be used, what validation studies are available, and how is risk to the patient minimized? Statistically, good estimates of variability are needed because compositing averages out valuable variation.

**Summary**

Composite sampling may be acceptable when the material is known to be homogeneous or the variability structure is well estimated with high confidence. It is a bad approach, however, when used for critical materials, APIs, or in the absence of information about variability of the material.

Composite sampling is not prohibited by FDA, but it is suspect from the get go. It must be supported by data, facts, and documentation.
New First-to-File Patent Rule Threatens Open Collaboration

Steve Berry

New US patent rules change the playing field for open innovation.

Collaboration and innovation go hand-in-hand in the pharmaceutical industry. New patent rules, however, are posing a threat to Big Pharma’s partnership efforts.

The Leahy-Smith America Invents Act (AIA), the first significant amendment to the US patent system in 60 years, is causing anxiety and speculation across the pharmaceutical industry. The AIA, which was signed into law in September 2011, went into full effect March 16, 2013 when its most controversial aspect was enacted: patents will now be awarded to the “first-to-file” rather than to the “first-to-invent” individual, company, or other institution (1).

Provisions of the new law

The law was enacted to cure a variety of ills in the US patent system, but among its main objectives was to streamline the patent system, reduce patent litigation, and bolster innovation. The new law is a good, incremental step in these directions, but it may also create unintended impacts. The first-to-file rule has corporations and inventors concerned about expanded opposition procedures that will increase challenges to patents as well as the possible chilling effect on collaborations that fuel new product development.

In the past, inventors could have years to develop and garner funding for patent filings. Under the new law, however, they will be forced to file patent applications quickly or risk losing claim to their inventions. This means the race to file likely will compromise an inventor’s ability to create high-quality and defensible patents. Larger pharmaceutical companies will likely experience a deepening fear of divulging or receiving too much proprietary information when partnering with smaller entities and independent innovators. This fear could affect the quantity and quality of new products developed in the pharmaceutical industry as well as other patent-driven industries.

Corporate America has been riding the trend of open innovation, in which companies have opened themselves up to soliciting and receiving ideas from individuals and organizations outside their own companies to stock their new-product pipelines. Companies that built and operate effective open-innovation capabilities have by and large gained an advantage over their competitors. Unfortunately, provisions under AIA could greatly narrow the aperture of open innovation programs and limit the potential return to the company and the inventor.

Overcoming the challenges

Unintentionally, the AIA has provided added motivation for all inventors to be secretive regarding their innovation efforts to avoid tipping off another party that may outrace them to a patent filing. The new law allows inventors to publish the details of their inventions up to one year before filing the patent application, thereby protecting the invention for that time period. There are, however, significant drawbacks. By publishing before filing the patent application, the inventor loses the advantage of competitive stealth within the US and forfeits ownership rights outside the US, given that most other countries consider published details of innovations as public domain. Additionally, publishing before filing may be viewed negatively by pharmaceutical companies considering a licensing or acquisition agreement because it may give an early warning to competitors. Pharmaceutical companies working with smaller organizations in an open-innovation program will want their collaborators to operate in secret as much as possible. Larger companies might restrict their collaborators from publishing their inventions early or requiring them to accept restrictive conditions before submitting ideas or innovations for consideration.

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Special Report: Interphex Conference

Facility Trends: Modularization and Single Use

Jennifer Markarian

Pharmaceutical Technology spoke with INTERPHEX 2013 conference-session presenters to gain insight on trends in facility and process design.

The conference schedule at INTERPHEX 2013 covered a wide range of topics, including facility and process design. Pharmaceutical Technology interviewed Craig Sandstrom, director of process engineering at Fluor; Par Almhem, president of ModWave and Modular Partners; and Jeff Odum, director of operations at IPS–Integrated Project Services, to gain their perspectives on trends in facility and process design.

Modularization

Modularization has been used by other industries for decades and, over the past few years, has been more accepted by the bio/pharmaceutical industry. Modularization is fast becoming an essential component of bio/pharmaceutical facility design. Use of modularization is growing because it meets the industry needs for reduced cost, accelerated construction schedules, and quality construction.

PharmTech: What are some of the considerations for using modularization?

Sandstrom (Fluor): Typically people have certain cost, schedule, and quality goals for their projects. Early on in a project, an effort is undertaken to look at the site and region where the facility will be constructed and also the facility design itself to determine what opportunities exist to address those cost, schedule, and quality issues.

Some of the local or regional issues include labor availability, labor rates, and associated logistics, such as what the site has in terms of being able to get people and materials to the site. Limitations in this area may drive a desire to try to move some of those activities offsite.

In addition, there is a desire to accelerate schedules. People want to make decisions and capital commitments as late as possible to save money and also to meet product demand, which causes project schedules to be increasingly compressed. One of the ways to address compressed schedules is via modularization. Modularization allows you to parallel path many of your activities, such as process-piping and equipment construction, and in parallel with some of the activities that take place to erect the building shell.

Finally, there are quality issues. Some places that you may want to build may not have quality labor resources available, or the weather or site conditions may be prohibitive. Moving the construction offsite allows you to do your construction in a better-controlled environment with higher-skilled labor.

PharmTech: What is involved in standardization of modular unit operations?

Almhem (Modular Partners): A module, in itself, is intended to be standardized. A module has a defined function with defined inputs and outputs. Once you identify a part of the process as a clear function with a clear input and output, you can design and build that as one unit. You can combine these units in different ways to create a variety of systems from a limited number of building blocks, which are the module units or unit operations. One example is a mixing skid, with the mixing system and controls all in one module.

PharmTech: What types of modules are used in pharmaceutical production?

Sandstrom (Fluor): One common type is the building module, in which all the architectural features, equipment, and piping are preinstalled. Another common use concept is the tank-array module, which may include several different process-unit operations in one module. There are many other varieties of modules. In piping-specific modules, for example, you modularize just the equipment, such as a pipe rack or a large cluster of instrumentation.

PharmTech: What do you see as the future of modular manufacturing?

Sandstrom (Fluor): I see modularization as an essential component of almost all facility designs. We see it now, and we see the trend continuing in the future.

One driver is that as facilities increasingly move to more remote locations, such as in Asia or South America where local trades aren’t as mature as they are in the US and Europe, there’s a desire to modularize to get the hygienic components of the facility designed and fabricated in a controlled-quality location.

Almhem (Modular Partners): Modularization doesn’t actually change the manufacturing itself; it’s more about how you manufacture. Modules will be used as the building blocks for more and more processes simply because it’s a more efficient way of building a process function, or indeed building almost anything. Nobody would consider building a software system any other way than using modules (or objects as they are called in software), for example. We will see more and more modular systems and modular pieces in pharmaceutical and biotechnology facilities and processes.

Implementing single-use systems in traditional stainless-steel facilities

PharmTech: What are some of the advantages of implementing single-use systems?

Odum (IPS): Advantages include reduction of cleaning costs via the decrease in the size or elimination of costly clean-in-place (CIP) systems because you are now getting away from fixed stainless steel equipment. Along that same line, there...
Future manufacturing systems must be agile enough to deliver on this flexibility with regards to a wider variety of product types and in a shorter timeframe. —Odum

Many developments in the biopharmaceutical industry have added to the challenges of designing, building, and operating the traditional manufacturing facilities that we’ve used over the past three decades. As our insights into product requirements and product characterization increase, the critical path for the development of many new products is now shifting to the process development stage, and manufacturing timelines are being condensed. Speed and flexibility are thus becoming crucial to many of our clients.

Future manufacturing systems must be agile enough to deliver on this flexibility with regards to a wider variety of product types and in a shorter timeframe. Single-use systems can provide a means to allow for this increased flexibility and a focus on speed to market, even if you are dealing with a stainless steel-based facility.

PharmTech: Who should consider implementing at least some single-use systems?

Odum: Implementing single-use technology must be driven by the product and process attributes, the need for flexibility, and an understanding of the critical process parameters. Any number of manufacturing organizations could benefit from the implementation of single-use technology.

One group that I think is going to see a significant benefit is contract manufacturers. Because their business model is driven by both speed and flexibility, single-use technology could provide some distinct advantages in terms of their ability to adapt to new processes based on not only new clients but existing clients. Single-use technology gives them the flexibility to change their platform technology rather rapidly and probably with a lower cost. Lower need for classified space would also decrease capital expenditures.

Other business models would also benefit from this type of technology. Organizations that are focused on process development, such as research-driven organizations that do high-level development work, would benefit. Manufacturers focused on pandemic response would benefit from the ability to adapt very rapidly. Flexibility and adaptability are crucial.

Another group that could benefit from single-use technology, in a way that perhaps they haven’t started to look at in depth, is the academic institutions, which are being squeezed by their ability to fund capital expenditures for facility infrastructure. Any manufacturing organization should really explore the potential advantages of this type of technology.

PharmTech: What are some of the unique challenges of implementing single-use systems, particularly when you have an existing stainless-steel facility?

Odum: We work with a number of clients who have a stainless-steel-based platform and are creating what we refer to as hybrid facilities. Three challenges stand out. First is a real understanding of the process definition and description. Although this may seem obvious, we have found that companies sometimes have a knowledge gap, especially from a developmental standpoint, on exactly how a specific process-unit operation may or may not be impacted by going to this technology.

The second challenge is looking at flows. Single-use systems are very flexible and modular in their approach from an equipment standpoint, and the ability to move components in and out of a particular space creates some logistical issues. As a part of that, there also needs to be a close investigation of accessibility. When your scenario includes a fixed stainless-steel asset that resides in a particular manufacturing suite—maybe due to size or maybe due to a future need—the ability for operators to access equipment and perform their day-to-day operations is extremely important.

The third challenge is process support. When you are dealing with single-use systems, you are now going to also deal with many single-use components that are absolutely necessary in order for each process unit operation to be executed and work the way it’s supposed to. Tubing sets, for example, are needed to connect components and allow the process to occur. Instruments, such as those to measure flow or temperature, must be integrated into the system.

The design and development of these support items becomes a complex effort because there are a lot of parts and pieces that are going to have to be put together. Some companies get outside vendors to do this for them. Others have chosen to do some of it internally, but it’s very different from designing a fixed piece of stainless-steel pipe in a building to run from point A to point B. Because of the fact that you’re dealing with tubing, you have issues with regards to accessibility and logistics. Where do these hang? How do you support them? How do you make sure that they do not get damaged, or stepped on, or run over during the movement of equipment?

Wrapping around all these issues is the idea of closure. One of the things that we pay very close attention to is the idea of looking at system-closure analysis to make sure that, as all these components are designed, we are doing everything that is necessary to, first and foremost, protect the product from any potential contamination source and, in doing so, making sure that the system components are designed properly so that this closure can be validated.

Single-use technology is not without its challenges, but these are challenges that are being addressed to create systems that are efficient and bring a much higher utilization to a facility.
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Outsourcing’s Modest Role as a Cost-Containment Strategy

Eric Langer

Outsourcing is weighing in more as a tactic for cost-cutting, but it is still not the primary weapon.

Companies are outsourcing now more than ever before, but there are indications that these choices are based on strategic calculi rather than as an actual cost-cutting mechanism, although cost is slowly entering more into the decision to outsource. Part of BioPlan Associates’ 10th Annual Report and Survey of Biopharmaceutical Manufacturers evaluated the ways in which companies are addressing cost issues in biopharmaceutical manufacturing (1). The study found that the most significant action taken in the past 12 months was the “implementation of programs to reduce operating costs,” indicated by 69.2% of respondents, down from 80.7% in 2012 and 73.1% in 2011. Various other activities, such as negotiating harder with vendors to reduce costs, implementing lean manufacturing programs, and accepting single-use systems into clinical manufacturing operations, were undertaken by at least one-third of respondents. Outsourcing to reduce costs, however, was not a key priority (1). Of the 19 cost-cutting actions examined in the study, the five actions relating to outsourcing occupied the bottom spots in the survey results, an indication that when it comes time to tightening the reins, calling a CMO is not the first option. In fact, it is one of the last.

Changing fortunes

That tendency, however, might be slowly changing. During the past several years, the percentage of respondents indicating that they outsourced activities as a cost-cutting mechanism has grown. The 2013 survey showed the following (see Figure 1):

- 16.8% of respondents in 2013 outsourced jobs in manufacturing, up from 14.4% in 2012 and 11.8% in 2011.
- 14% outsourced manufacturing to domestic service providers, an increase from 9.4% in 2012 and 7.1% in 2011.
- 13.3% outsourced jobs in process development, on par with the 13.3% in 2012 and 13.2% in 2011.
- 12.6% outsourced manufacturing to nondomestic service providers (offshoring), up from 9.4% in 2012 and 5.7% in 2011.
- 11.2% outsourced jobs in R&D, up from 9% the past two years.

The relatively low priority assigned to outsourcing as a cost-cutting tool may reflect companies viewing these activities more as means to fill temporary gaps in capacity and as a way for biopharmaceutical companies to focus on their core competencies. Another explanation may be that although outsourcing is seen as a useful cost-reduction tool, it does not compare as favorably with other cost-cutting tactics. Biopharmaceutical companies are not alone in this result; in previous BioPlan surveys, few vendors approached cost containment by outsourcing.

Figure 1: Percentage of respondents taking actions to reduce costs during the past 12 months, respectively in 2011, 2012, 2013.

<table>
<thead>
<tr>
<th>Outsourced jobs in manufacturing</th>
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<tr>
<td>Outsourced jobs in process development</td>
<td>13.3%</td>
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<td>Outsourced jobs in R&amp;D</td>
<td>11.2%</td>
<td>9.0%</td>
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<tr>
<td>Outsourced manufacturing to domestic service providers</td>
<td>9.4%</td>
<td>7.1%</td>
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<tr>
<td>Outsourced manufacturing to nondomestic service providers (offshoring)</td>
<td>12.6%</td>
<td>5.7%</td>
<td>9.4%</td>
</tr>
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Percentage of respondents

Eric Langer is president of BioPlan Associates, tel. 301.921.5979, elanger@bioplanassociates.com, and a periodic contributor to Outsourcing Outlook.
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Outsourcing Outlook

The data from 2013, however, show that outsourcing is increasingly considered as a cost-cutting mechanism. This trend may be related to CMOs expanding their manufacturing competence through novel technologies, single-use/disposable bioreactors, and other differentiated bioprocessing services. These expansions result in increased adaptability, lower costs, faster turnaround, and higher yields. These trends create greater competition among CMOs and more choice for biopharmaceutical companies. Increased competition that results in downward pricing pressures among CMOs might lead clients to more heavily figure cost into the decision when making a decision about outsourcing. When bio/pharmaceutical companies were asked about critical issues when considering outsourcing biomanufacturing to a CMO, 42% said it was “very important” that the CMOs demonstrate the cost effectiveness of their services. That percentage is the highest level of response to this factor since 2007, when it was also cited by 42% of respondents. In 2012, only 29% of respondents cited this factor as such.

Looking ahead
As technological improvements allow, suppliers and manufacturers are shifting their focus to reducing costs. Almost three-quarters (73%) of respondents in the 2013 study said that due to the recent global economic situation, they had placed a “much greater” or “somewhat greater” focus on cost-cutting, up from 67% in 2012 and approximately 71% in 2011 and 2010.

Production-capacity constraints continue to shift, and these changes require manufacturers to scrutinize costs and technology. CMOs continue to offer valuable technical expertise and flexible capacity that supports biotherapeutic developers and reduces the total risks associated with building (or not) internal capacity.

Moreover, under extreme conditions, activities such as R&D, which were considered essential to retain in-house, may become options for outsourcing. Biopharmaceutical companies plan for the long term, and because R&D cycles and production build-outs are lengthy and risk-intensive, it is the additional benefits that outsourcing can bring to drug development and manufacture that often swing decisions.

For several years, BioPlan has seen that general budgets for in-house biopharmaceutical manufacturing have risen more quickly than budgets for outsourced manufacturing. This trend suggests that as budgets expand for other activities, biomanufacturers want to maintain their outsourcing spending levels, perhaps in an attempt to extract more value out of their relationships. Although outsourcing may not be a primary cost-cutting tool, it is subject to similar efficiency pressures.

In 2013, budgets for outsourced bio-manufacturing are expected to rise by an estimated 1.7%, up from -0.4% in 2012, 0.8% in 2011, -1.2% in 2010, and -1.3% in 2009. It is interesting to see budgets rise at the same time as more biomanufacturers look to outsourcing as a cost-cutting mechanism. This trend may be an indication that clients will be outsourcing more activities this year, not only to benefit from the additional capabilities of today’s sophisticated CMO, but also because they believe they will realize some cost savings from their decisions.

Reference

Industry Perspectives – cont. from page 74

Although the AIA presents challenges, there are ways in which it can co-exist with collaborative, open-innovation programs. The key to success is an open-innovation management system that both controls the flow of information and also prevents the disclosure of confidential information. This system protects the inventor submitting the idea as well as the pharmaceutical company and provides intellectual property security. When managed well, open innovation-based partnerships function as symbiotic business relationships where the parties support each other in making the new invention a profitable venture. The past 10 years have shown that the ideas of many are better than the ideas of a few, and such an approach can facilitate more efficient development of technology.

The new first-to-file environment need not increase anxiety for large pharmaceutical firms nor smaller entities about protecting patents and developing intellectual property. Bilaterally secure open-innovation programs create an environment through which corporations and independent inventors help shield each other from the side effects of the new US patent law. This result is best achieved through dedicated systems that offer secure gateways for information, an automated submitter communications process and other processes, such as screens, filters, and analytics to protect both parties without requiring restrictive confidentiality conditions. Corporations can even leverage open innovation to conduct “prior art” searches without the risk of contaminating intellectual property, which helps create more defensible patents and prepare for potential challenges.

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Cyclica and Dalton Agree to Identify and Develop New Drug Candidates

Cyclica, a company that develops indexed biological databases and software for the pharmaceutical and biotechnology industries, and the CDMO Dalton Pharma Services have formed an agreement to identify and develop new drug candidates designed to apply computational molecular designs to medicinal-chemistry and drug-development services.

The collaboration will consist of Cyclica’s in silico drug-design and optimization services and provide access to the company’s databases to be applied to several lead molecules previously developed by Dalton Medicinal Chemistry, as well as additional compounds. Dalton Pharma Services will synthesize and manufacture quantities of selected drug candidates in its licensed facilities, for analysis and consideration by a leading global pharmaceutical company’s candidate screening program. The assets developed through this agreement will be equally owned by the parties.

Med Opportunity Partners Acquires Ferro Pfanstiehl

Med Opportunity Partners (MEDOP), a private equity firm focused on the healthcare sector, has acquired Ferro Pfanstiehl Laboratories, a provider of cGMP carbohydrates and API products and services, from Ferro Corporation. As a result of the acquisition, Ferro Pfanstiehl Laboratories was renamed Pfanstiehl.

“We are excited to invest in Pfanstiehl at this time,” said Jim Breckenridge, MEDOP founding member and new Pfanstiehl chairman. “The US global biopharmaceutical market is expected to exceed $100 billion by 2015 and requires high purity functional excipients to meet increasing quality, regulatory and service requirements. Pfanstiehl is well positioned to be a major beneficiary of this overall shift toward high purity cGMP excipients utilized in biopharmaceutical formulation and manufacturing processes. We plan to invest in Pfanstiehl to expand the company’s participation in these compelling sectors.”

Catalent Applied Drug Delivery Institute Names New Life-Sciences Leader

The Catalent Applied Drug Delivery Institute has appointed Dr. Ralph Lipp as the founding member of the institute’s advisory board. Dr. Lipp brings over 20 years of industry and academic experience to the Institute, having previously served as vice-president, pharmaceutical sciences R&D at Eli Lilly and Company, and in R&D leadership roles at Schering. Dr. Lipp’s accomplishments include more than 20 patents, including 5 marketed medicines, and more than 100 additional scientific publications. His research experience includes oncology, cardiovascular disease, central nervous system disorders, women’s health, in vivo diagnostics, and dermatology.

Stuart E. Needleman, President and Chief Operating Officer, Aptuit

PharmTech: Can you explain Aptuit’s capabilities and how it integrates its services across its network?

Needleman: We have API chemistry manufacturing and a business that does solid-state analysis (i.e., the bridge between the formula API manufacturer and formulation development). We have a sterile fill-finish business in the early phase of Phase I, proof-of-concept capabilities, small-dose, as well as a large-scale internal capability, and an R&D engine that we acquired from GlaxoSmithKline in Verona, Italy, which includes integrated drug development, discovery through to dosage form, including toxicology and chemistry.

PharmTech: What are some of the key trends influencing pharmaceutical outsourcing overall, and in the specific sectors of Aptuit services, like formulation, development, and API manufacturing?

Needleman: There is a restructuring that will continue to go on inside big pharma as they focus on their sites, their facilities, their overheads, and their pipelines. There is some turmoil in the internal pharma R&D; and we want to make sure that we are there to serve those clients as they go through those restructuring and potentially rebalance their portfolio.

We also want to make sure we’re following the pipelines of the emerging pharmaceutical companies because, again, innovation continues to come from the smaller companies. We want to make sure we meet the needs of where we see the industry going whether it’s therapeutic areas, or whether it’s going to be much more focused on oncology in the high potency areas. We want to make sure that we’re meeting the market needs or the market demand. We also want to understand where the market is heading and be able to offer services, technologies, and capabilities to meet those needs.

For example, if it’s going to be in the prefilled syringe area, we want to make sure we’re making investments in that. We have created a scientific advisory board internally made up of some of our leading scientists around our network to discuss the future direction of technology, market, and commercial needs, so we’re prepared to evaluate and build strategies around our clients’ needs.
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GE Healthcare’s line of disposable Cellbag bioreactor chambers includes optical pH patch and ReadyMate aseptic connectors. Cellbag bioreactors range in size from 2 to 200 L. The units are designed to simplify pH monitoring and making aseptic connections, thus eliminating the need for insertions and connections. The chambers are available in standard off-the-shelf and custom designs. GE Healthcare • www.gethealthcare.com • tel. +46 018 612 00 00

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Contract manufacturing services
Through its predecessor, AbbVie has more than 120 years of experience in developing and producing pharmaceutical products. For more than 25 years, the company has offered contract manufacturing to provide customers with high-quality, innovative, cost-effective services in the area of biologics, potent, drug product, and bulk APIs to benefit the companies that put their trust in us. AbbVie, North Chicago, IL • www.abbviecontractmfg.com

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

Contract development and manufacturing services
Patheneon is a provider of contract development and manufacturing services to the global pharmaceutical industry, providing products and services to approximately 300 of the world’s leading pharmaceutical and biotechnical companies. Through its fully integrated worldwide network, it ensures that customer products can be launched anywhere in the world. Patheneon, Research Triangle Park, NC • www.patheneon.com • tel. 905.821.4001

Manufacturing and raw-material testing
Incorporating its Avrio parenteral manufacturing facility into the Irvine brand in January was the first step in Irvine’s three-prong initiative for aggressive yet stable growth: more highly trained technical personnel, new instrumentation and increased capacity for formulation, biopharmaceuticals, and raw-material testing. Irvine Pharmaceutical Services, Irvine, CA • www.irvinepharma.com • tel. 877.445.6554
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Drug-development services
Vetter’s development service provides support for drug-development projects from inception to market launch. The services include clinical manufacturing at facilities in Chicago and Europe with scale-up and transfer to Vetter’s large-scale manufacturing facilities. The services provide primary- and secondary-packaging development, process development, clinical manufacturing, pharmaceutical analysis, and regulatory affairs services. Vetter Pharma International USA, Skokie, IL • www.vetter-pharma.com • tel. 847.581.6888

Fill/finish services
CANGENE bioPharma provides fill/finish services for vials and syringes. The company’s services are performed in compliance in accordance with US, EU, and Japanese regulations. The company produces more than 25 commercial and 185 clinical products for customers for distribution in more than 50 countries. CANGENE bioPharma, Baltimore, MD • www.cangenebiopharma.com • tel. 800.441.4225

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Laboratory services
Eurofins Lancaster Laboratories works with clients in the biopharmaceutical industry to advance candidates from development through commercialization, ensuring regulatory compliance, cost effectiveness, and achievement of timelines. The company has facilities in Pennsylvania, Michigan, and Ireland, and offers five service models, including professional scientific staffing and full-time equivalent programs. Eurofins Lancaster Laboratories, Lancaster, PA • www.lancasterlabspharma.com • tel. 717.656.2300

Development and manufacturing services
UPM Pharmaceuticals provides contract drug development, cGMP manufacturing, and analytical testing services. The company specializes in the administration of solid oral-dosage forms. UPM’s scientists have experience with product development challenges such as low-dose content uniformity, high-dose compressibility, and controlled drug-release rates. UPM Pharmaceuticals, Baltimore, MD • www.upm-inc.com • tel. 410.843.3738

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**Lyophilization: a primer – cont. from page 45**

Where primary drying should end and secondary drying begin is dependent on the individual properties of the product and the stated process requirements. But as the two stages are so different in processing terms, when and how the change should occur is of vital importance to the success of the process and minimizing cycle time.

The end of secondary drying, and the freeze-drying process overall, is difficult to define and pinpoint. A range of tolerance for final moisture content must be decided upon, weighing the desired stability and activity of the product against the cost of continuing the process for further hours or days.

A conservative freeze-drying cycle that has been arrived at by trial and error might produce satisfactory product reliably and repeatably. However, there will be no scientific evidence of the suitability of the process other than exhaustive quality assurance testing. By providing evidence of the analysis, cycle feedback and overall process of cycle development, the suitability of the cycle can be easily verified by internal and external auditors.

In the instance that previously robust batches lose consistency or product stability slips, the original data can be used for troubleshooting.

Freeze-drying cycles are optimized not only with regards the formulation, but also the freeze drying equipment and batch parameters such as fill depth, batch size, and container type. For optimum efficiency in manufacturing scale-up, the cycle should be designed for the specific process equipment used.

The following real example of how this technology has been used to improve efficiency speaks volumes about how much of a difference characterizing a freeze-drying cycle makes.

A vaccines manufacturer had a 70-hour freeze-drying cycle for a product, which was limiting manufacturing capability. Freeze-drying company Biopharma Technology Ltd was asked to analyze the product’s thermal characteristics. The cycle had been designed to freeze the product below -45 °C and maintain the product below -40 °C throughout primary drying. FDM analysis showed a collapse temperature at -18.2 °C; DTA/impedance analysis showed a significant softening event at -23 °C. Raising the designated freezing temperature to a still-conservative -28 °C enabled the freezing step to be significantly shortened, as well as saving the cost in energy of cooling the chamber and product through unnecessary extra degrees. The temperature setpoint of primary drying could also be raised to increase the rate of sublimation. Process monitoring subsequently indicated that the product was being left in primary drying conditions for much longer than necessary and the duration of this stage was cut by 40%.

Analysis of the product dried using the new cycle demonstrated that while the total process time was reduced by 15 hours, the product was just as good as before.

**References**

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FDA Expectations for Supplier Management

James Stumpff, Principal Consultant at PAREXEL discusses supplier management and FDA’s expectations.

Q. How can FDA-regulated industries best manage their suppliers? What does FDA expect?

A. A robust system for the continual management of FDA-industry suppliers is necessary to assure the safety, identity, strength, quality, and purity of drug products. FDA’s long history offers many examples of serious impact to consumers, patients, and marketed products, resulting from inadequate management of suppliers. These quality issues can range from uncontrolled supplier changes that result in material not meeting intended specifications, to non-conforming product or components that pose serious health hazards. Comprehensive, far-reaching, and continuous supplier oversight will minimize the risk of such incidents and ensure sustainable quality and cGMP compliance.

FDA’s Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, and the International Conference on Harmonization (ICH) Q10 Pharmaceutical Quality System documents provide guidance related to the control of outsourced operations (1, 2). In addition to providing general supplier management direction to the industry, these guidance documents point to FDA’s expectations with respect to ongoing monitoring of key suppliers. Essentially, FDA considers suppliers an extension of the sponsor, insofar as ensuring goods and services meet pre-established specifications, such that finished product integrity can always be maintained.

Procedures related to the qualification of suppliers, and in some cases quality agreements, are essential components of a meaningful supplier-management program. These procedures must be sufficiently detailed to ensure adequate control of the materials and supply chain. The initial qualification of a supplier will typically consist of an onsite assessment of the supplier, along with characterization and qualification of the supply. Once qualified, the quality agreement provides the basis from which on-going supplier management is achieved.

The supplier quality agreement will provide details related to periodic audits, re-evaluation, even probation conditions of the supplier. It should also require that any subsequent outsourcing decisions, or changes that the supplier intends to initiate, are brought to the attention of the sponsor, for their ultimate review and approval. Although FDA has never stated this specifically, the extent of oversight provided to suppliers should be commensurate with the risk posed by that material, component, or service. FDA’s stated emphasis on risk assessment and mitigation is consistent with this perspective.

Procedures related to the qualification of suppliers are essential components of a meaningful supplier-management program.

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, Section 703, requires that excipient manufacturers be identified in the drug listing (3). Section 711 requires oversight of materials used to manufacture drugs and drug products. FDA expects that meaningful quality agreements will be secured and that periodic audits will be conducted, as needed, to ensure sustainable compliance against the cGMPs and the Sponsor’s quality agreement. The frequency of these audits should be based on the compliance history of the supplier, and as stated above, the criticality of the supply. At the very least, crucial suppliers, such as API and container/closure suppliers, must be thoroughly evaluated with onsite assessments and frequent surveillance audits. Ongoing surveillance audits can be relaxed if, and only if, the supplier has not breached the quality agreement and does not pose a risk. FDA observations typically associated with supplier management include the lack of quality agreements, particularly for crucial suppliers, the lack of or inadequate supplier audits, and the lack of adequate follow-up to supplier issues.

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2. ICH, Q10, Guidance for Industry Q10 Pharmaceutical Quality System (ICH, April 2009).

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